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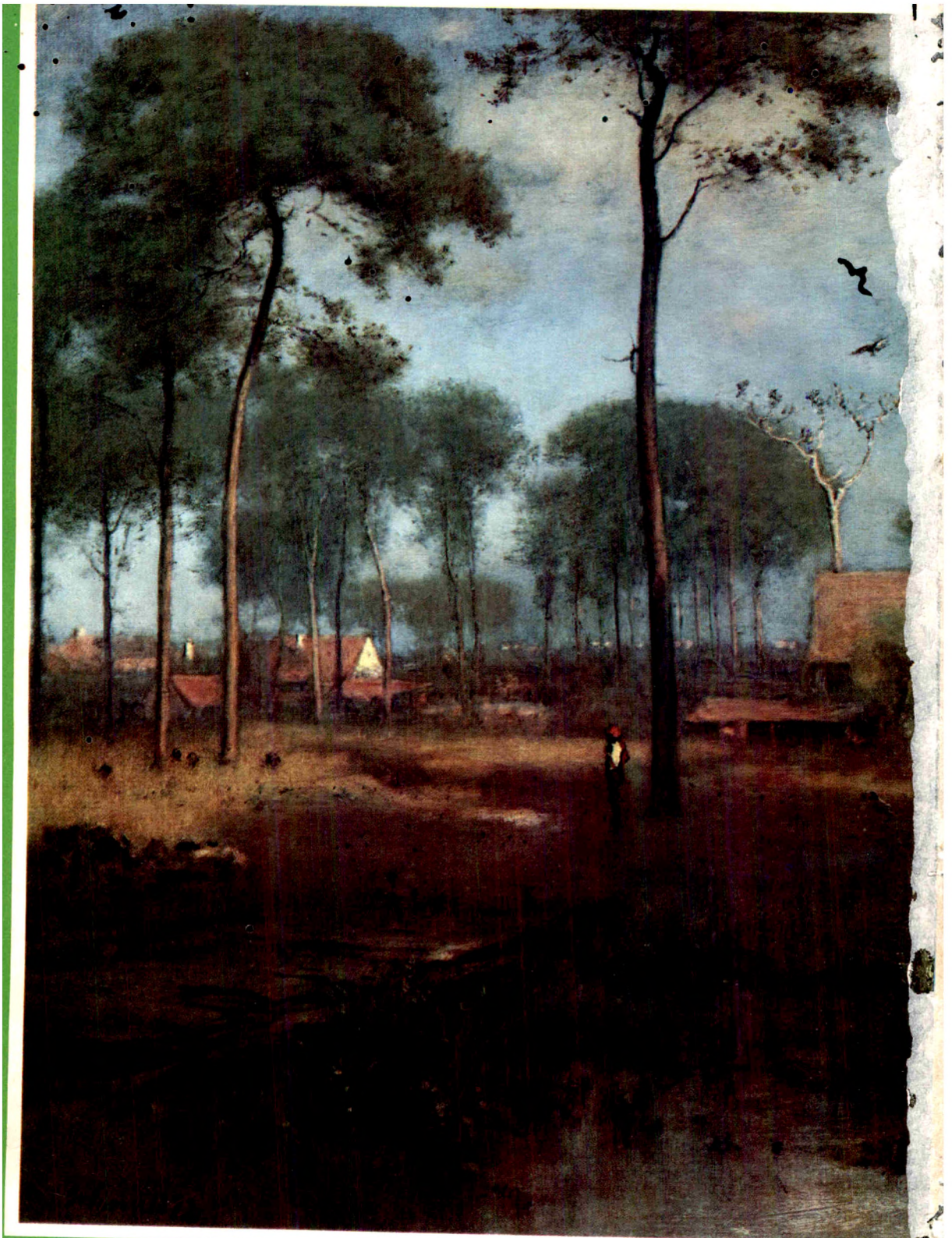

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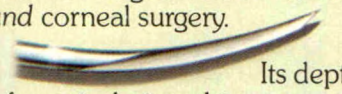

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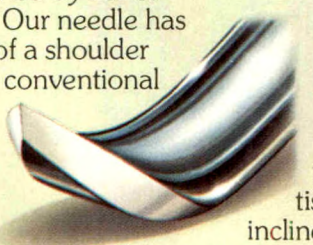

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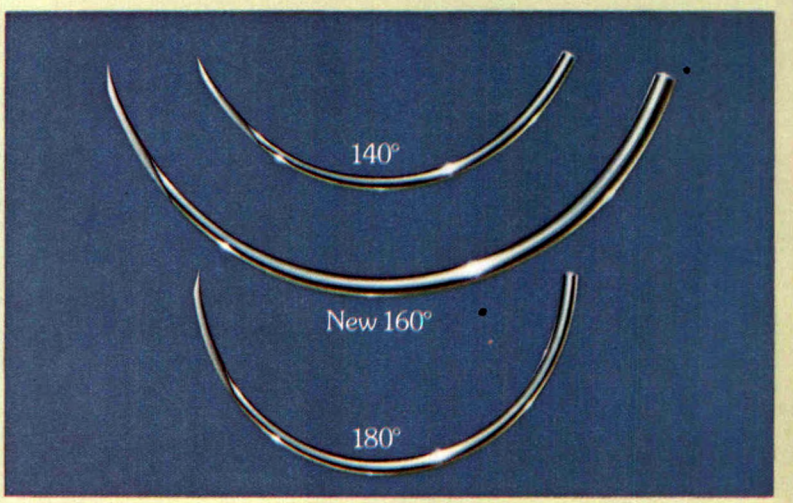

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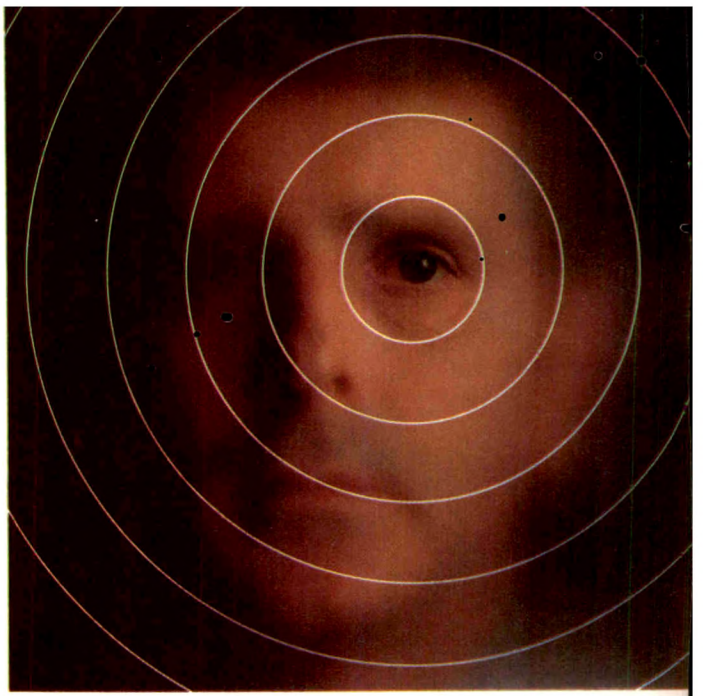
Epinephrine: in simple (open angle) glaucoma, a traditional therapy of choice



- First Line therapy: unlike pilocarpine, epinephrine does not produce miotic blurring. Unlike beta blockers, epinephrine provides efficacious therapy at minimal patient prescription costs.
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Warnings: Should not be employed where the nature of the glaucoma has not been clearly established. Contraindicated in narrow angle glaucoma. Use with caution in hypertension. Maculopathy with associated decrease in visual acuity may occur in the aphakic eye. If this occurs, discontinue administration promptly.

Adverse Reactions: Prolonged use may produce extracellular pigmentation in the palpebral conjunctiva which is innocuous. On rare occasions, systemic side effects have been observed. These include occipital headaches, palpitation, paleness, acceleration of heartbeat, trembling and perspiration.

Dosage: One or two drops in each eye, preferably at bedtime or as directed. The frequency of instillation should be titrated tonometrically to the individual response of each patient. This requires direct and continuous medical supervision. When used in conjunction with miotics, the miotic should be instilled first.

EPPY/N. In simple (open angle) glaucoma, the preferred epinephrine.

[1] Boger, WP: Timolol: Short Term "Escape" and Long Term "Drift." ANN OPHTH 11:8(1239) 1979.
[2] Thomas JV, Epstein DL: Transient Additive Effect of Timolol and Epinephrine in Primary Open-Angle Glaucoma. Glaucoma Clinical Research Center, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston Mass.
[3] Fraunfelder FT et al: Research Leads to More Effective Ways of Administering Eyedrops. JAMA 236: 21 Nov 22 1978.

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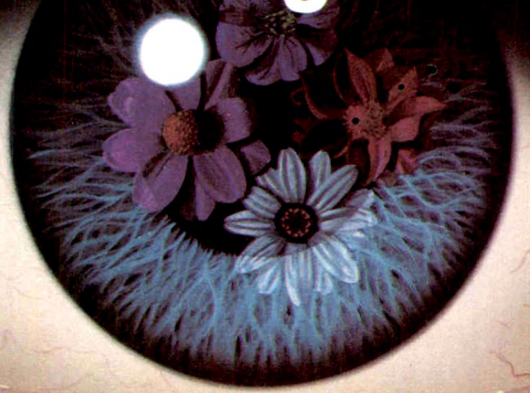
Treat the troublemakers in sight



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References:
1. Dorsch, W. and Thygeson, P. The clinical efficacy of medrysone, a new ophthalmic steroid. Am J Ophthalmol 65(1):74-75, 1968. 2. Thorson, J.C. and Eriksen, S.P. Anti-inflammatory properties of medrysone in external ocular inflammations. Am J Ophthalmol 71(4):844-846, 1971. 3. Bedrossian, R.H. and Eriksen, S.P. The treatment of ocular inflammation with medrysone. Arch Ophthalmol 81:184-191, 1969.

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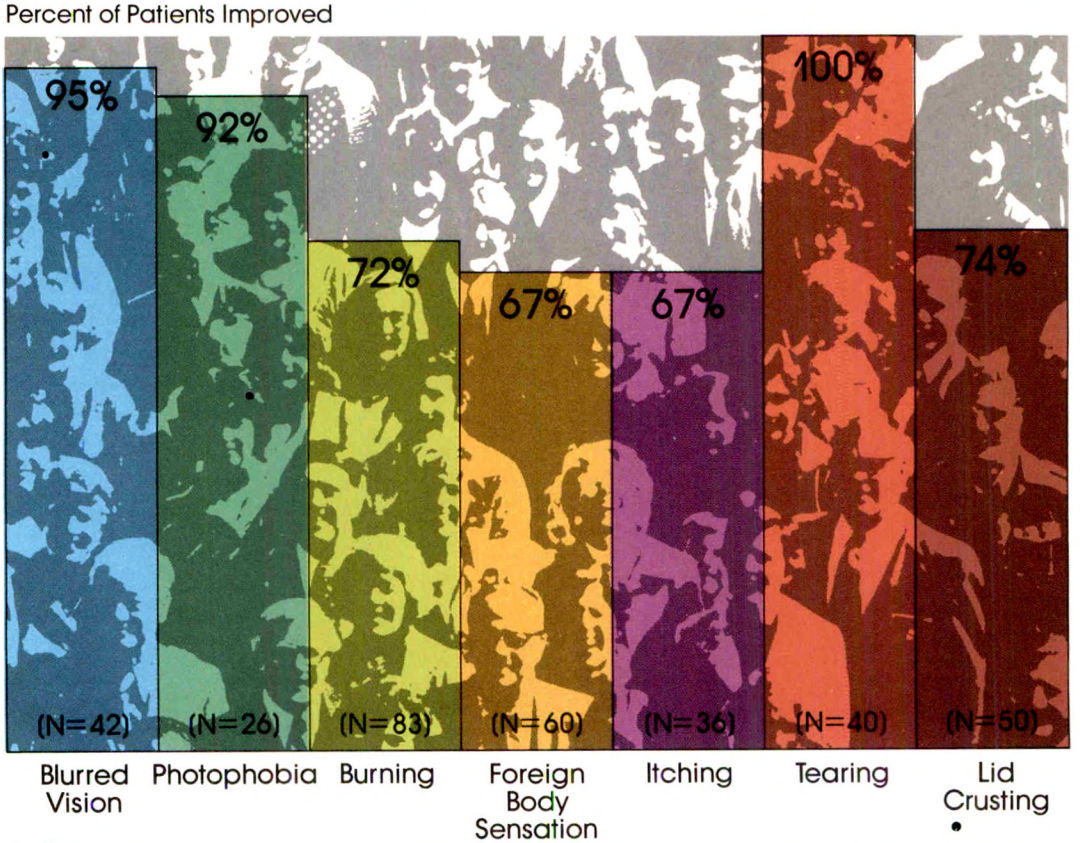

1. Clinical study data on file at SMP.
2. Gilbard JP, Farris RL, Santamaria J: Osmolarity of tear microvolumes in keratoconjunctivitis sicca. Arch Ophthalmol 96: 677-681 (1978).

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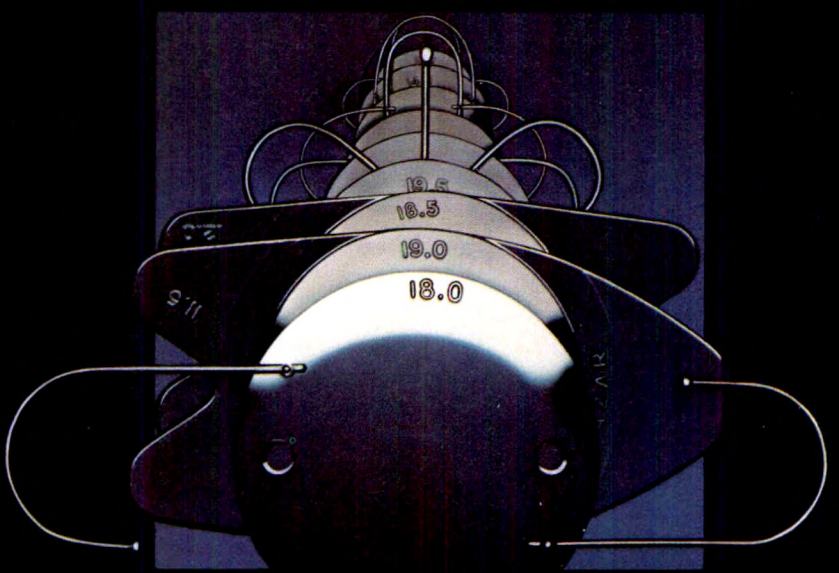

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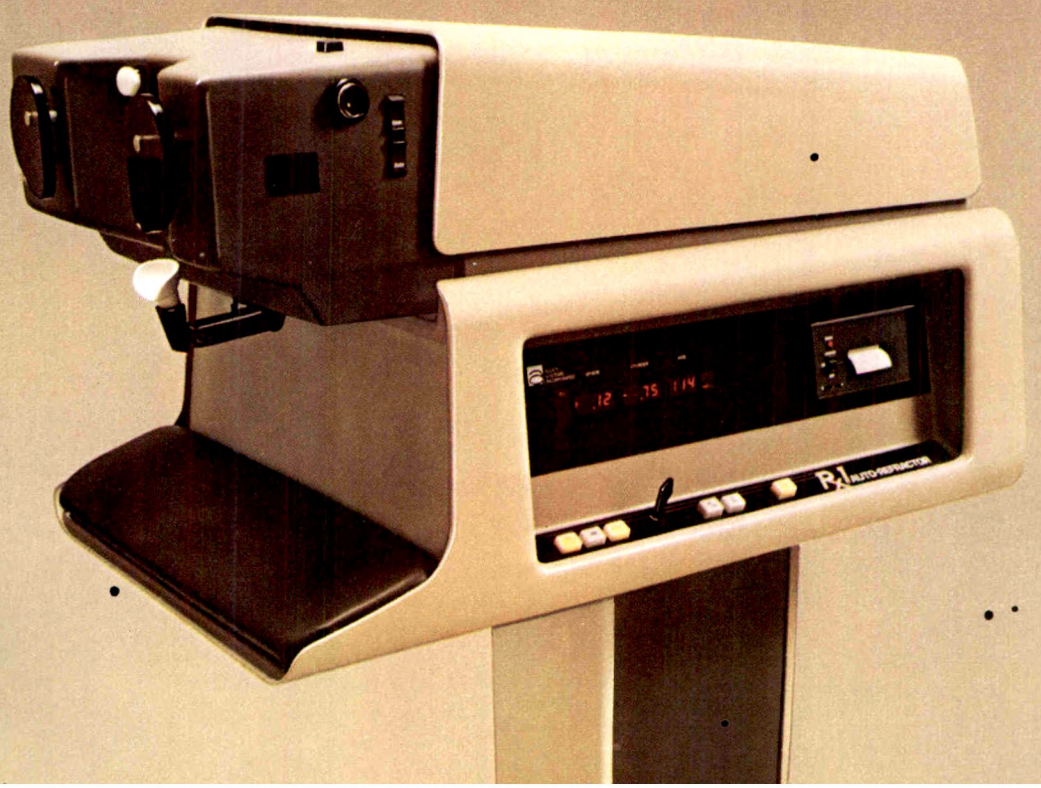

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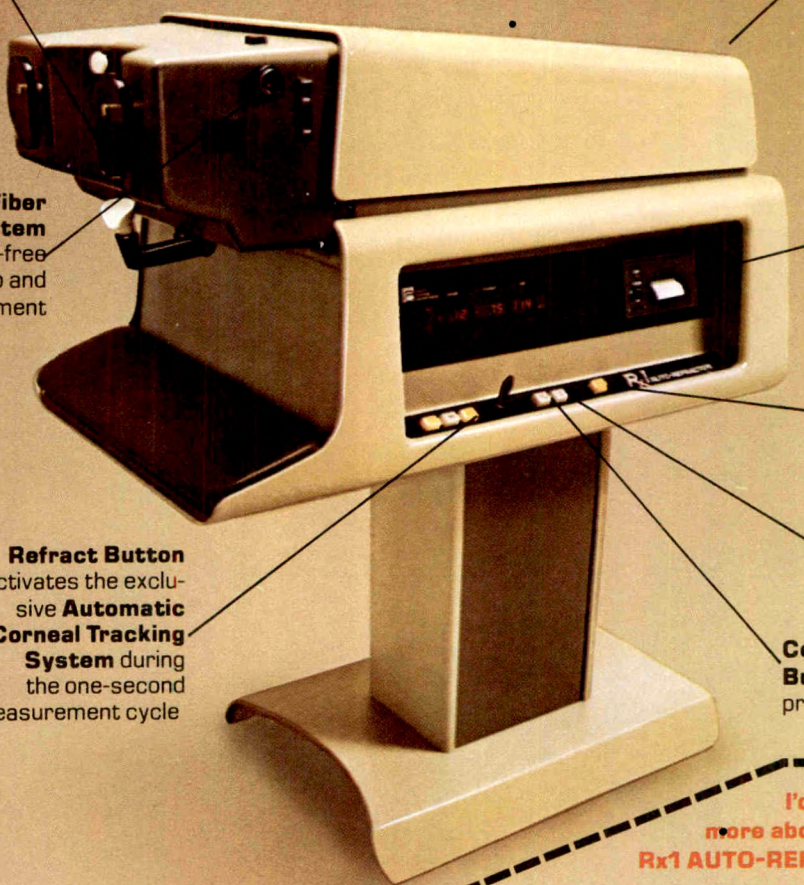

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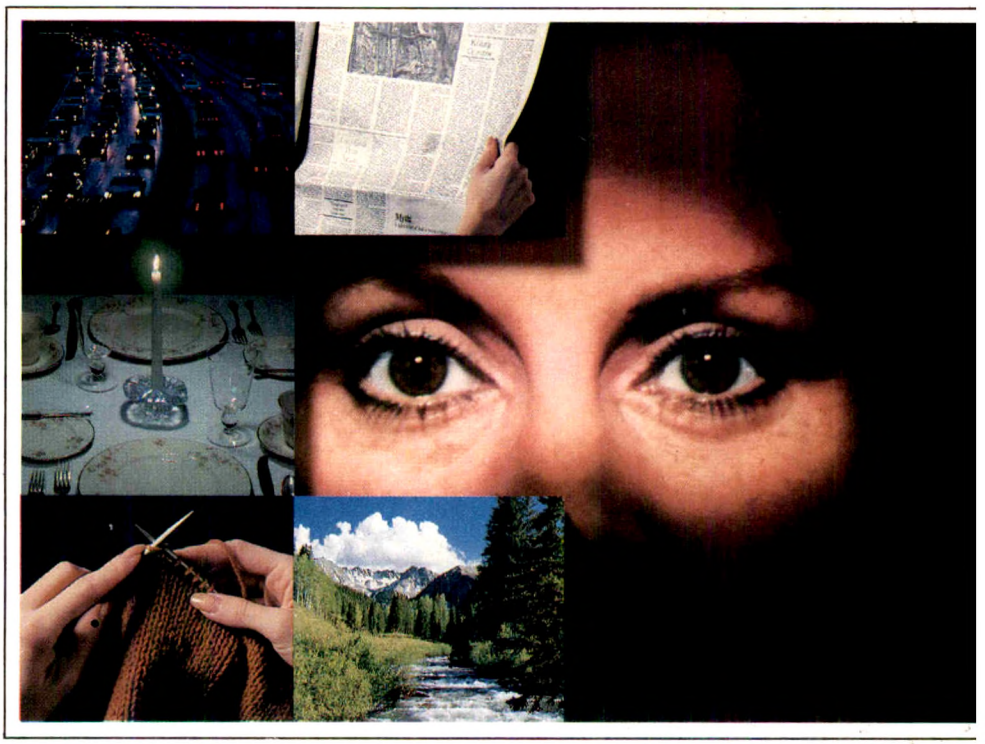
In chronic open-angle glaucoma therapy

Two good reasons to switch patients to



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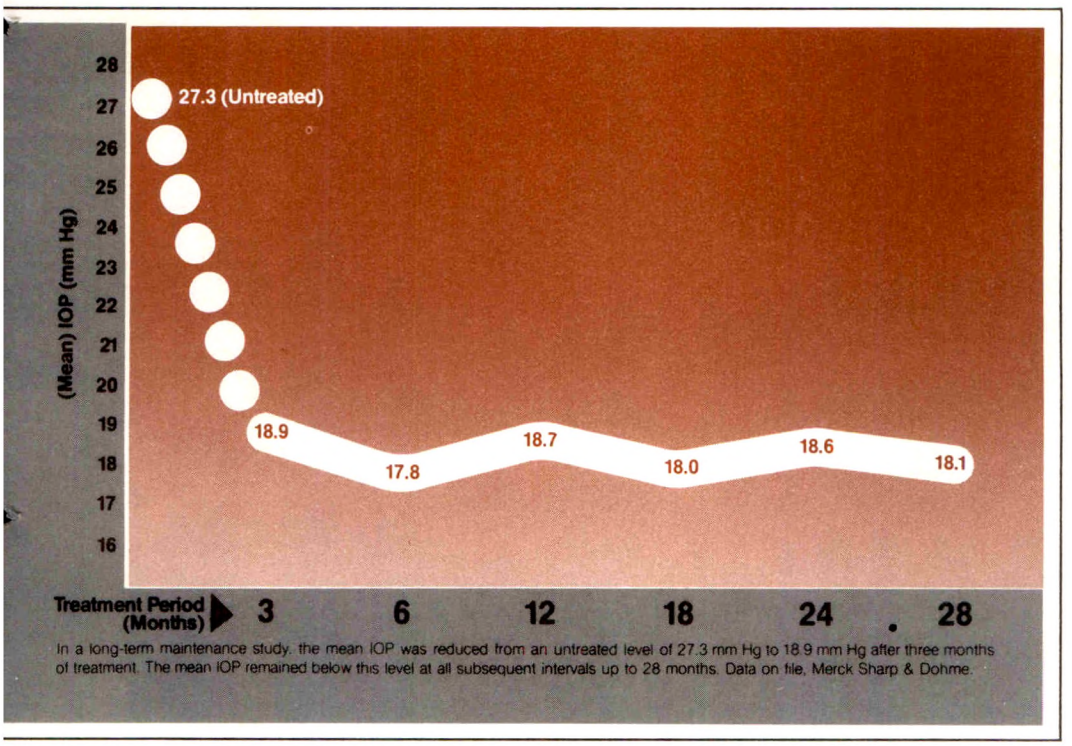

In a long-term maintenance study, the mean IOP was reduced from an untreated level of 27.3 mm Hg to 18.9 mm Hg after three months of treatment. The mean IOP remained below this level at all subsequent intervals up to 28 months. Data on file, Merck Sharp & Dohme.

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*Based on controlled multiclinic studies, evaluating over 1000 patients.

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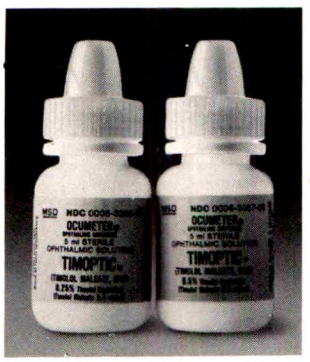

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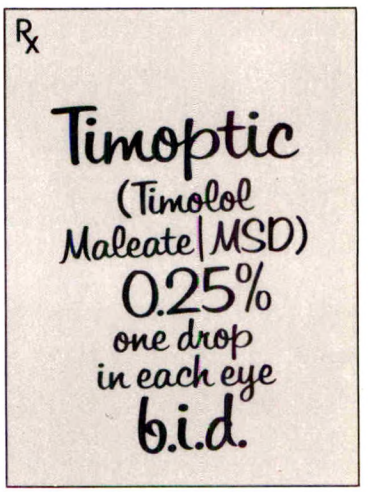

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.

Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.

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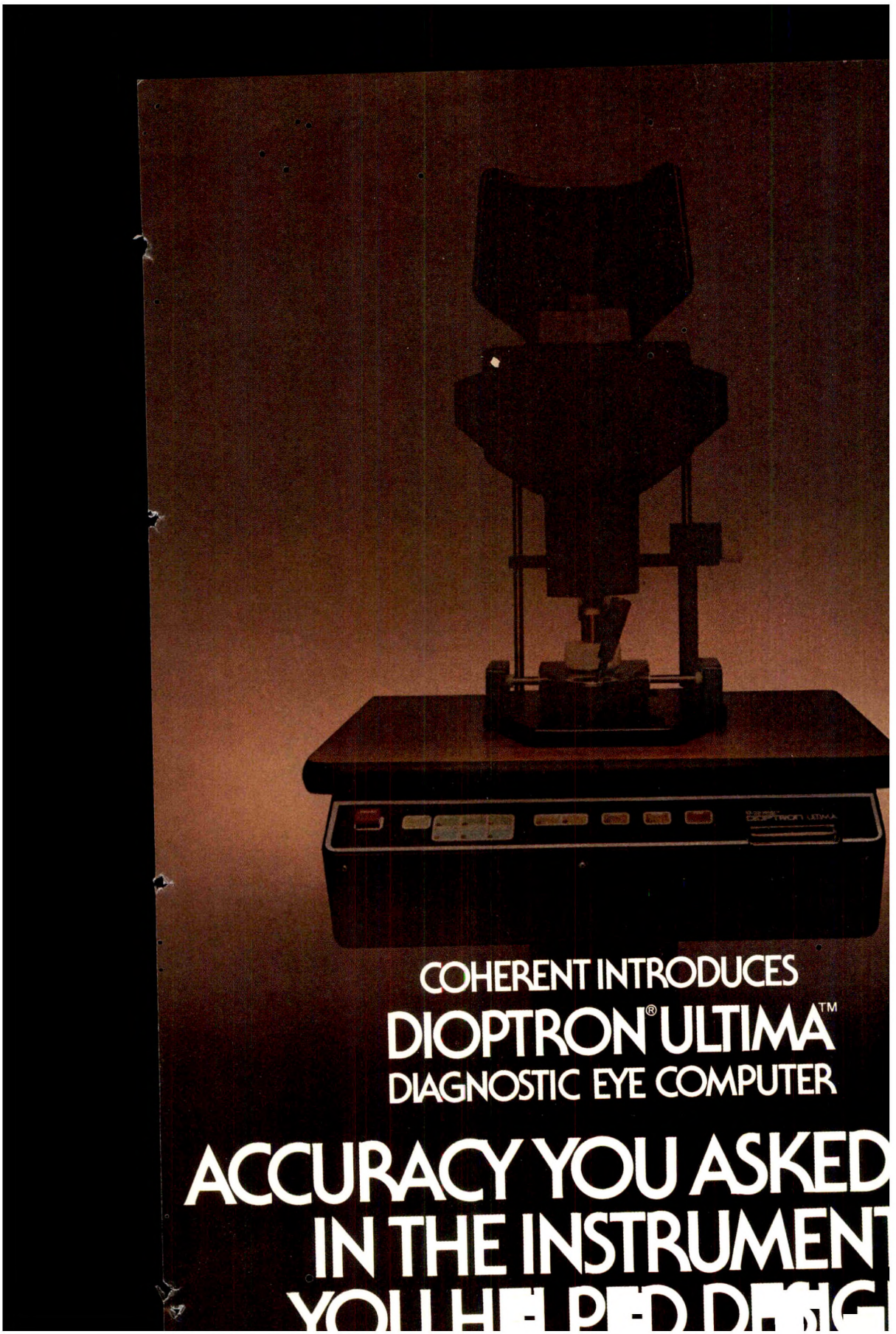
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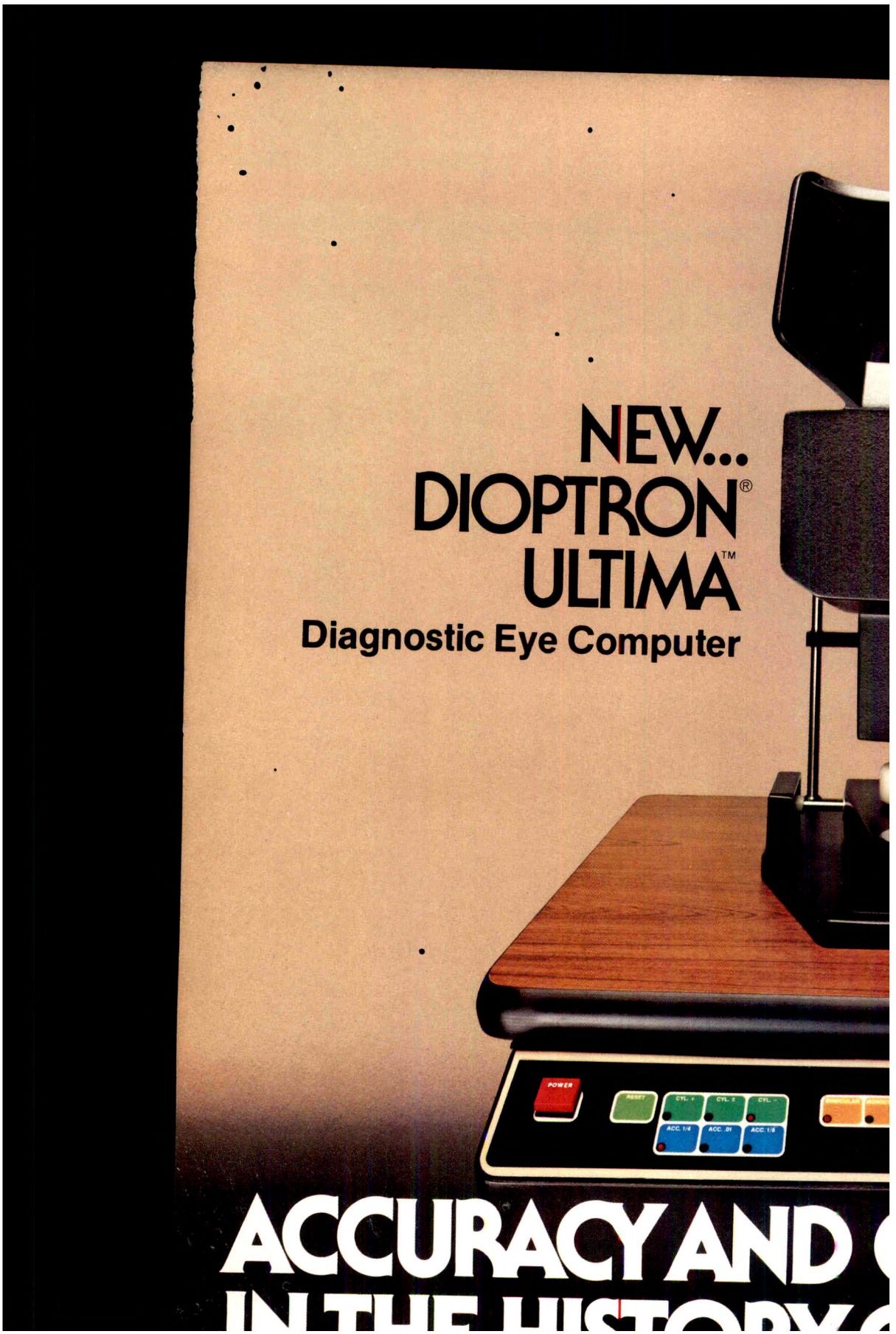
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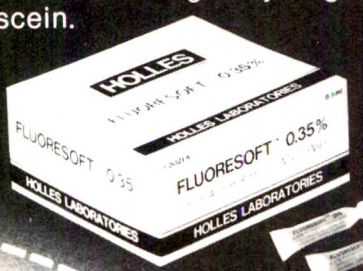

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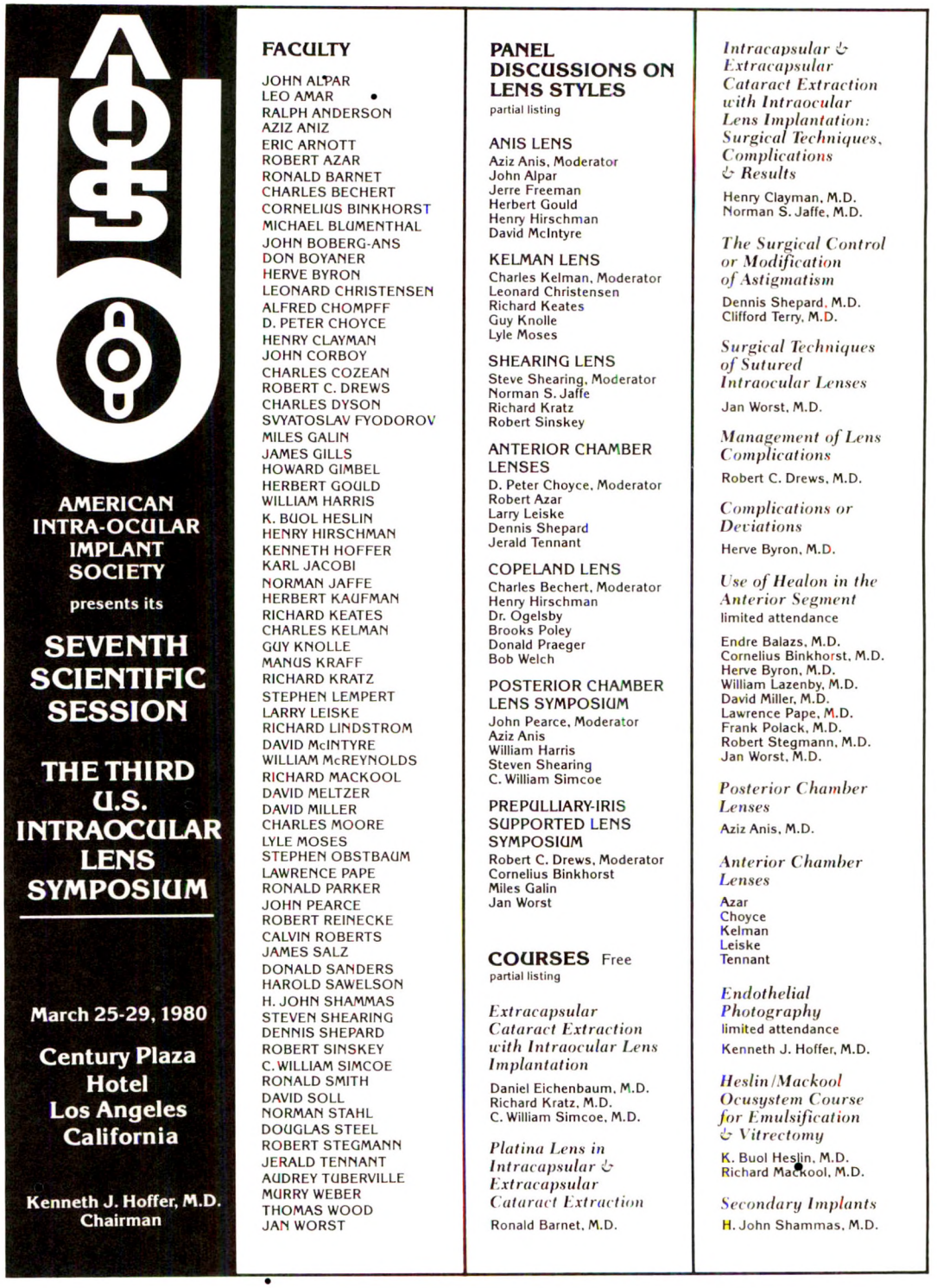

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Wednesday, March 26

Surgery Techniques

Intracapsular
Miles Galin, M.D.

Extracapsular
David McIntyre, M.D.

Phacoemulsification
Charles Kelman, M.D.

Vitrectomy
K. Buol Heslin, M.D.

Doing the Doctor's Paperwork
Dennis Shepard, M.D.

Eye Anatomy
Stephen Obstbaum, M.D.

Pre-Op Evaluation & History
Henry Clayman, M.D.

Lens Calculation
John Shammas, M.D.

Endothelial Photography
Manus Kraff, M.D.

Panel Discussion/ Question & Answer Period
Manus Kraff, M.D.
Moderator

Friday, March 28

Post-Operative Complications – Immediate & Future Treatment
Richard Kratz, M.D.

Post-Operative Care & Instruction
Murry Weber, M.D.

Psychological Needs of the Post-Op Patient
John Alpar, M.D.

Secondary Implants
John Darin, M.D.

Indications/ Contraindications
Norman Jaffe, M.D.

Surgical Complications
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*Nurses' and technicians' fee includes attendance at general sessions, lunches, etc., as well as special Nurses' and Technicians' Course.

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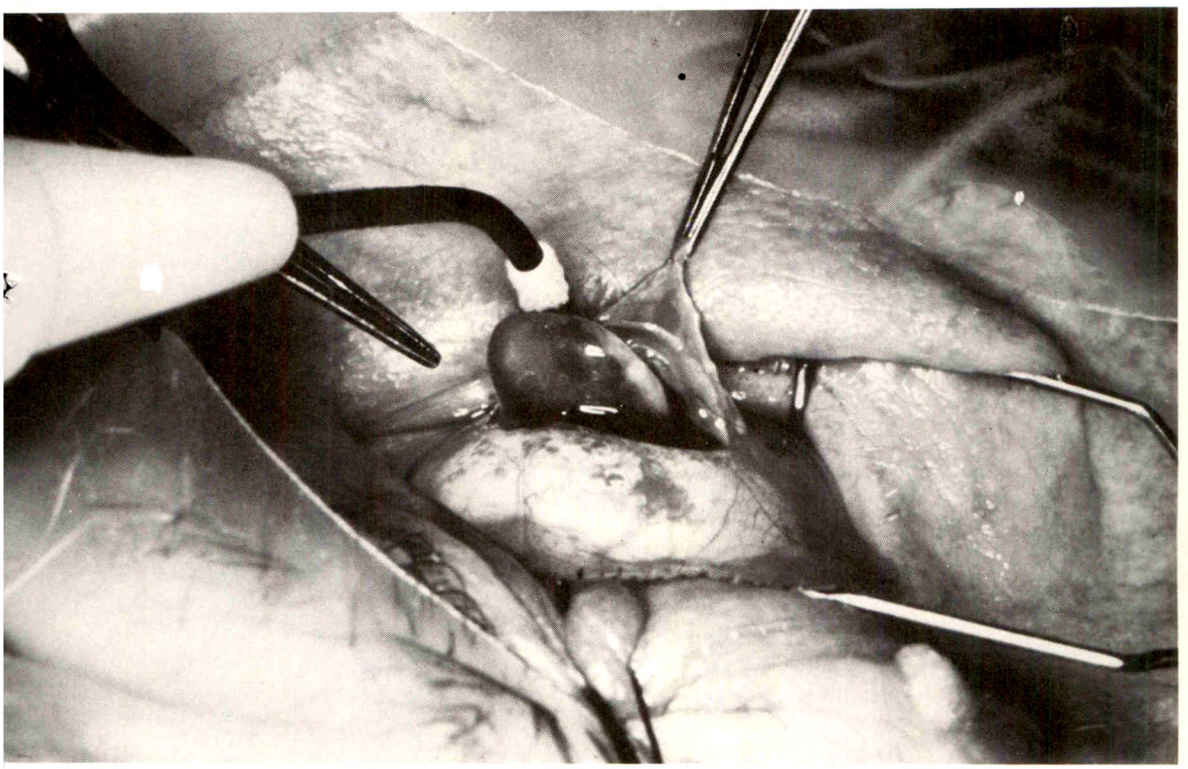

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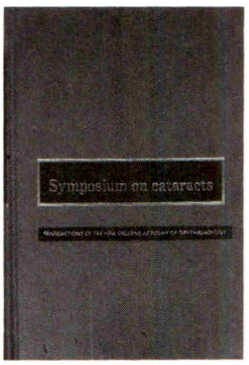

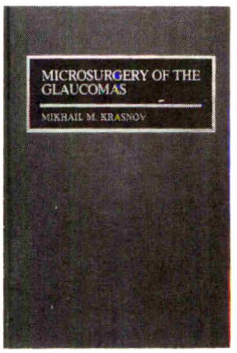

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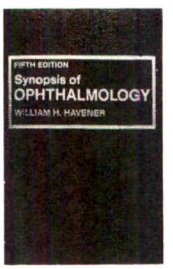

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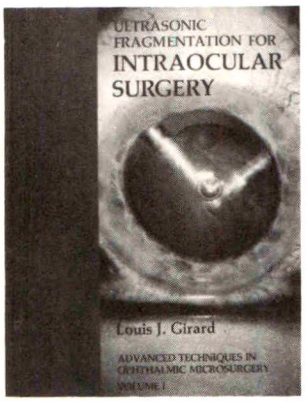

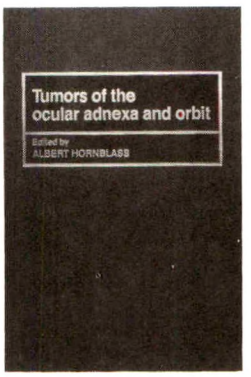

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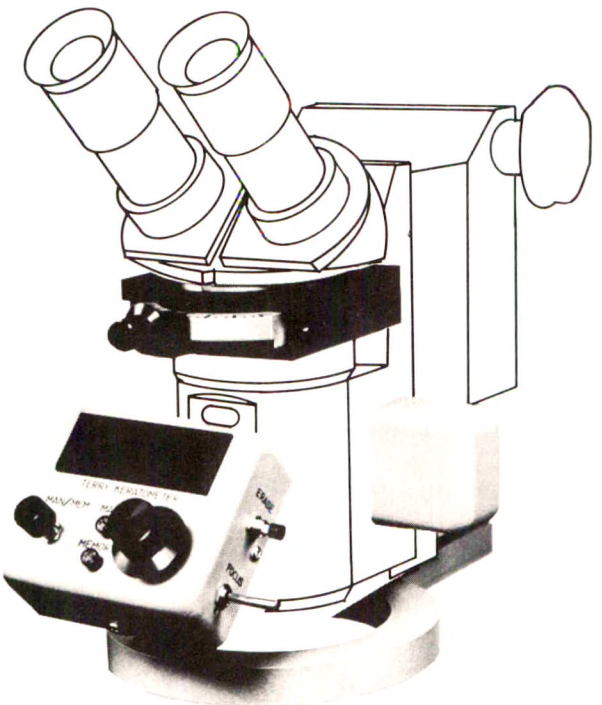

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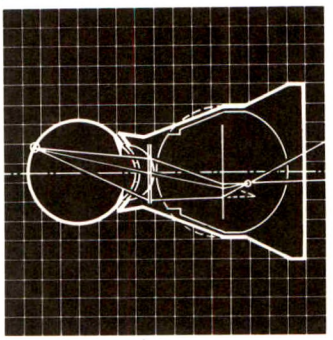

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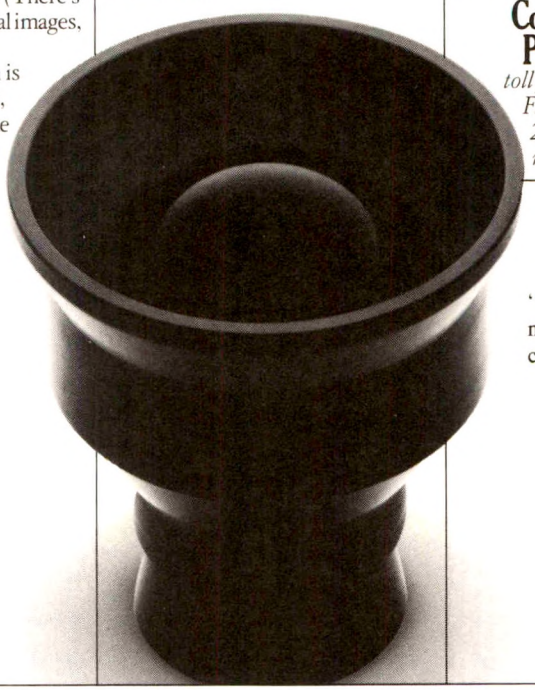

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Description. Vira-A (vidarabine, adenine arabinoside, or Ara-A) is an antiviral drug for topical ophthalmic administration. The chemical name is 9-β-D-arabinofuranosyladenine. Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

Clinical Pharmacology. Vira-A is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Except for Rhabdovirus and Oncornavirus, Vira-A does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

The antiviral mechanism of action has not been established. Vira-A appears to interfere with the early steps of viral DNA synthesis. Vira-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of Vira-A. Because of the low solubility of Vira-A, trace amounts of both Vira-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of Vira-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, Vira-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, Vira-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit.

Indications and Usage. Vira-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. Vira-A is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions to idoxuridine have occurred. The effectiveness of Vira-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous Vira-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone, have been administered concurrently with Vira-A Ophthalmic Ointment, 3%, without an increase in adverse reactions.

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If Vira-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

Vira-A is not effective against RNA virus or adenoviral ocular infections. Vira-A is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Contraindication. Vira-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. ***Use in Pregnancy:*** Vira-A (vidarabine) parenterally is teratogenic in rats and rabbits. Ten percent Vira-A ointment applied to 10% of the body surface during organogenesis induced fetal abnormalities in rabbits. When 10% Vira-A ointment was applied to 2 to 3% of the body surface of rabbits, no fetal abnormalities were found. This dose greatly exceeds the total recommended ophthalmic dose in humans. The possibility of embryonic or fetal damage in pregnant women receiving Vira-A (vidarabine ophthalmic ointment), 3%, is remote. The topical ophthalmic dose is small, and the drug relatively insoluble. Its ocular penetration is very low. However, a safe dose for a human embryo or fetus has not been established. Consequently, Vira-A should be used only when clearly indicated.

It is not known whether Vira-A is excreted in human milk. As a general rule, because many drugs are excreted in human milk, nursing should not be undertaken while a patient is under treatment. However, excretion of vidarabine in breast milk is unlikely because Vira-A is rapidly deaminated in the gastrointestinal tract.

Mutagenic Potential: Results of *in vitro* experiments indicate that vidarabine can be incorporated into mammalian DNA and can induce mutation in mammalian cells (mouse L5178Y cell line). Thus far, *in vivo* studies have not been as conclusive, but there is some evidence (dominant lethal assay in mice) that vidarabine may be capable of producing mutagenic effects in male germ cells.

It has also been reported that vidarabine causes chromosome breaks and gaps when added to human leukocytes *in vitro*. While the significance of these effects in terms of mutagenicity is not fully understood, there is a well-known correlation between the ability of various agents to produce such effects and their ability to produce heritable genetic damage.

Oncogenic Potential: Chronic parenteral (IM) studies of vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant increase in liver tumor incidence among the vidarabine-treated females. In the same study, some vidarabine-treated male mice developed kidney neoplasia. No renal tumors were found in the vehicle-treated control mice or the vidarabine-treated female mice.

In the rat study, intestinal, testicular, and thyroid neoplasia occurred with greater frequency among the vidarabine-treated animals than in the vehicle-treated controls. The increases in thyroid adenoma incidence in the high-dose (50 mg/kg) males and the low-dose (30 mg/kg) females were statistically significant.

Hepatic megalocytosis, associated with vidarabine treatment, has been found in short- and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.

The recommended frequency and duration of administration should not be exceeded (see Dosage and Administration).

Precautions. The diagnosis of keratoconjunctivitis due to Herpes simplex virus should be established clinically prior to prescribing Vira-A Ophthalmic Ointment, 3%.

Patients should be forewarned that Vira-A Ophthalmic Ointment, 3%, like any ophthalmic ointment, may produce a temporary visual haze.

Although viral resistance to Vira-A has not been observed, this possibility may exist.

Adverse Reactions. Lacrimation, foreign-body sensation, conjunctival injection, burning, irritation, superficial punctate keratitis, pain, photophobia, punctal occlusion, and sensitivity have been reported with Vira-A Ophthalmic Ointment, 3%. The following have also been reported but appear disease-related: uveitis, stromal edema, secondary glaucoma, trophic defects, corneal vascularization, and hyphema.

Overdosage. Acute massive overdosage by oral ingestion of the ophthalmic ointment has not occurred. However, the rapid deamination to arabinosylhypoxanthine should preclude any difficulty. The oral LD_{50} for vidarabine is greater than 5,020 mg/kg in mice and rats. No untoward effects should result from ingestion of the entire contents of a tube.

Overdosage by ocular instillation is unlikely because any excess should be quickly expelled from the conjunctival sac. Too frequent administration should be avoided.

Dosage and Administration. Administer approximately one half inch of Vira-A Ophthalmic Ointment, 3%, into the lower conjunctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or complete re-epithelialization has not occurred by 21 days, other forms of therapy should be considered. Some severe cases may require longer treatment.

After re-epithelialization has occurred, treatment for an additional seven days at a reduced dosage (such as twice daily) is recommended in order to prevent recurrence.

How Supplied. N 0071-3677-07 (Stock 18-1677-139)

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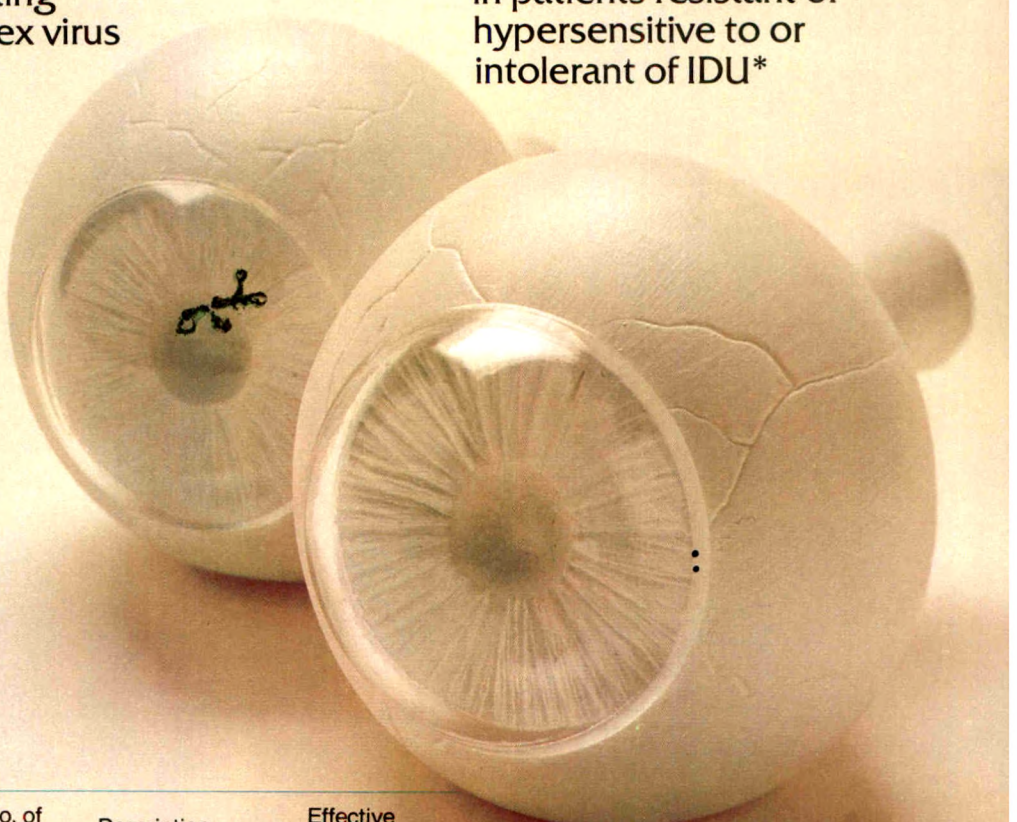

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a-A ntrolled Trials	81	Previously untreated	70 subjects **(86%)**
a-A controlled Trials	142	75% had been resistant or hypersensitive to IDU	101 subjects **(71%)**

TE: In the controlled and uncontrolled trials, 70 and 101 subjects, pectively, re-epithelialized at the end of three weeks on Vira-A.

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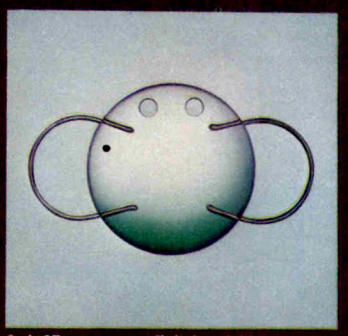

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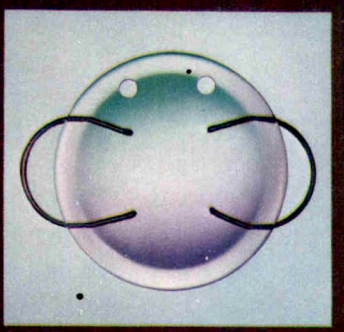

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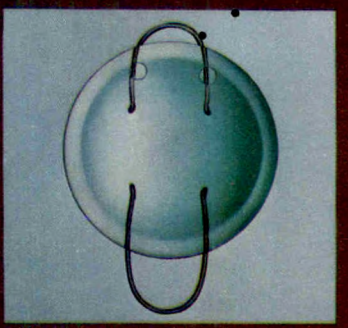

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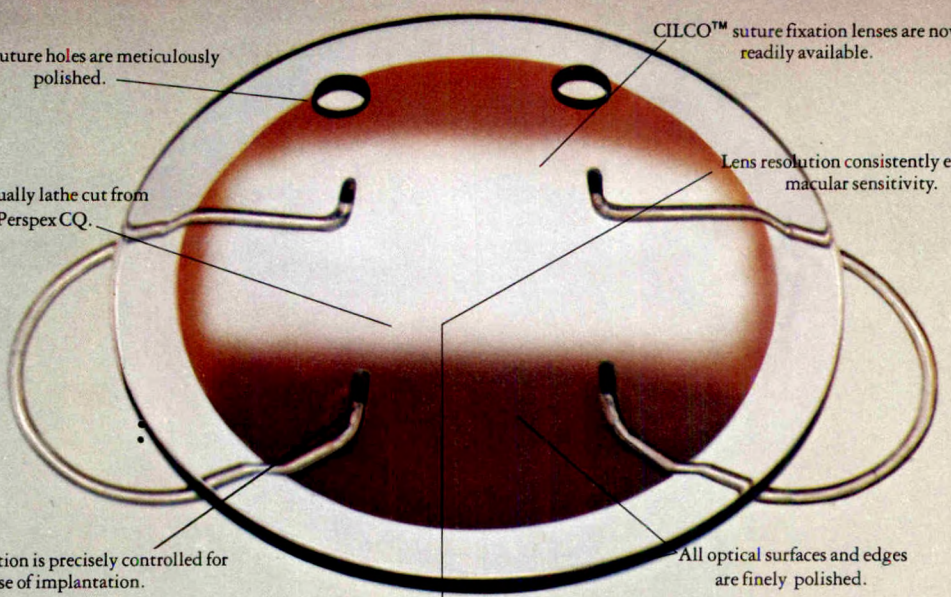

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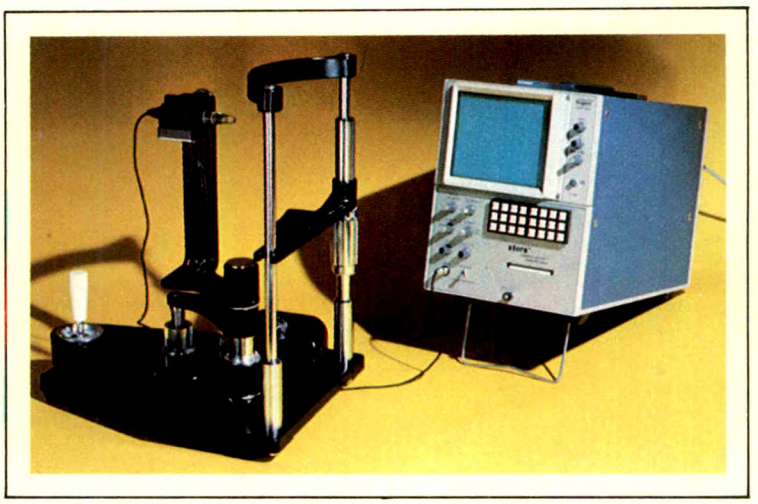

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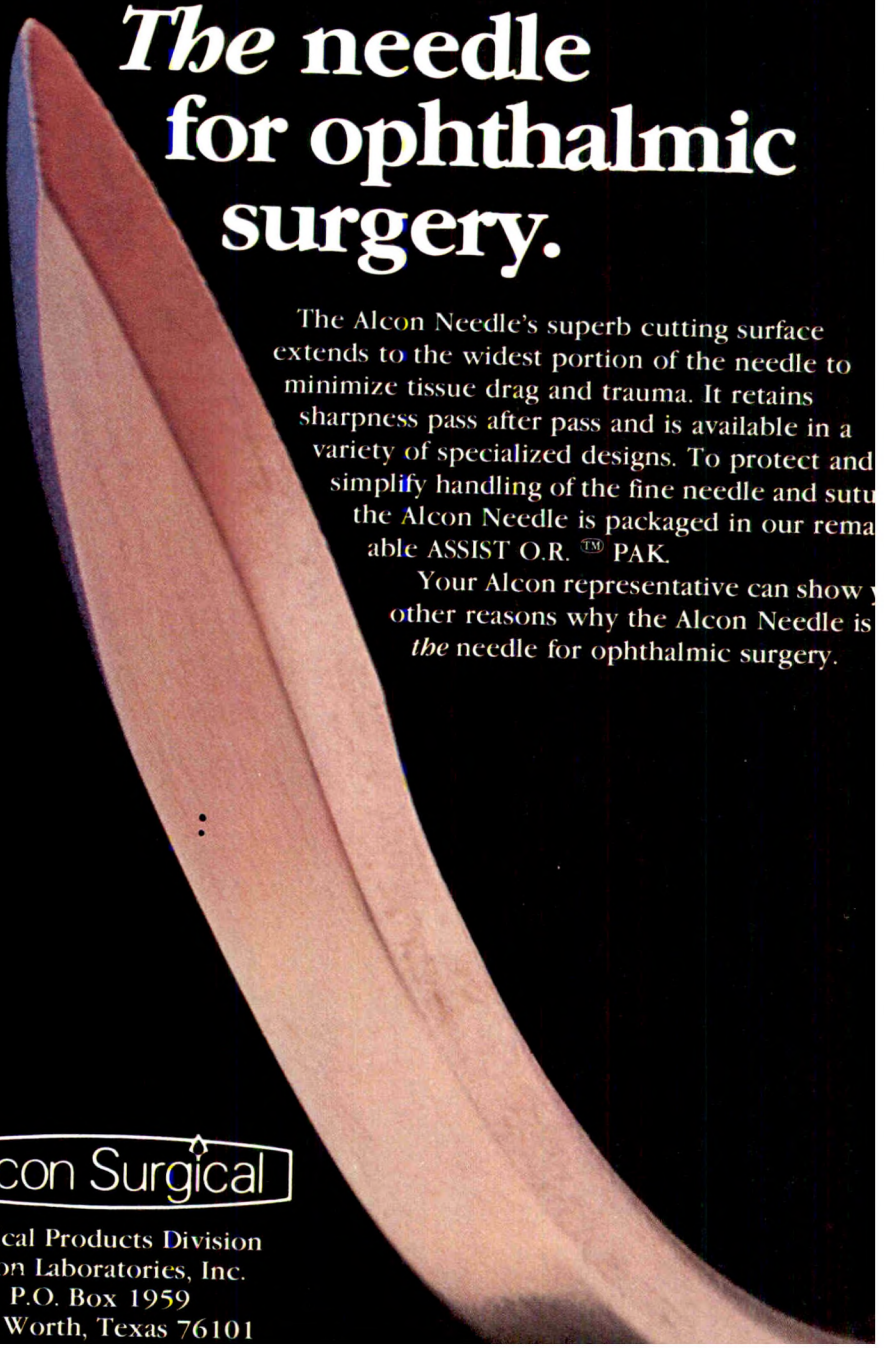

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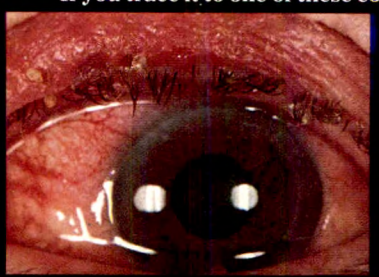

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Effective treatment for conjunctivitis, corneal ulcer and other infections due to susceptible microorganisms, such as *Staphylococcus aureus*

Ophthalmic Solution—a sterile, isotonic preparation containing 4% (40 mg/ml) sulfisoxazole diolamine—generally avoids significant stinging or burning

Ophthalmic Ointment—also containing 4% sulfisoxazole diolamine—provides more sustained contact with the ocular infection and is particularly appropriate for nighttime therapy

A Brief Summary of the product information, below, provides precautions and contraindications

Main photo taken with the Carl Zeiss photo slit lamp.

Dosage and Administration: Solution 2-3 drops in eye 3 or more times daily. Take care not to contaminate dropper. Ointment, small amount in lower conjunctival sac 1-3 times daily and at bedtime.

How Supplied:

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

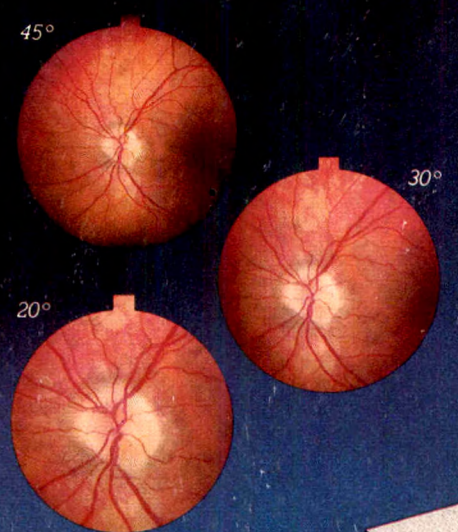
Variable Angle at the Flip of a Switch

The Versatile Topcon TRC-W Retinal Camera

Once again Topcon moves forward the art of fundus photography. With a variable angle camera that lets you instantly switch between three different settings —45,° 30,° and 20° —for maximum operating flexibility.

The TRC-W produces superior fluorescein angiograms of the fundus *or* iris. At the specific magnifications that meet your needs, with correct exposure control maintained throughout the magnification range. Two standard camera bodies are supplied for color documentation or fluorescein. Or choose the optional Polaroid back.

You'll find the TRC-W's price equally accommodating to your needs. Available with 2 or 3 frame per second power supplies; standard or tilt models.



TOPCON

A New World of Precision Optics

Topcon Instrument Corp. of America, 9 Keystone Place, Paramus, New Jersey 07652

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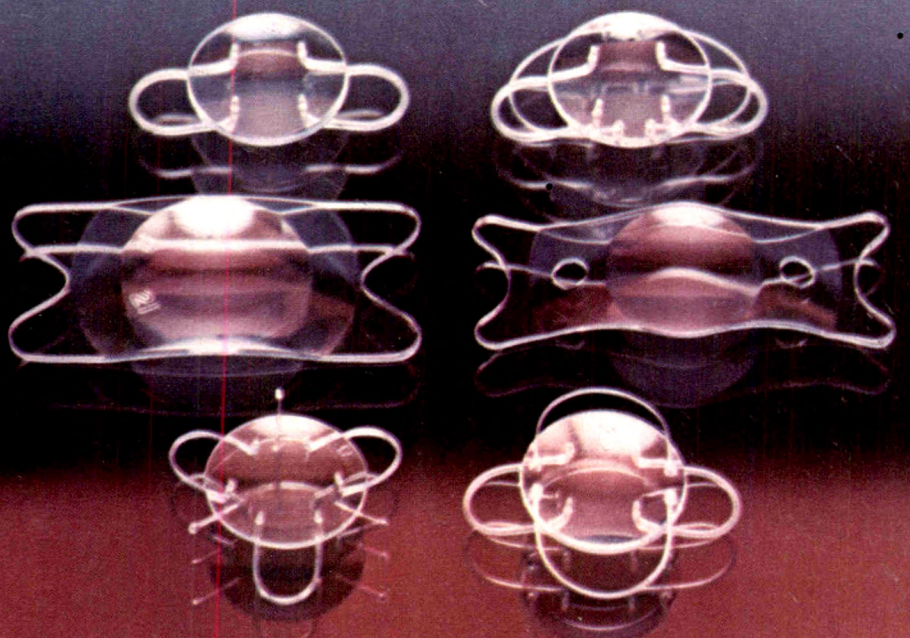

For quality lenses, backed by years of intraocular experience and dependable service, there's only one logical choice: Coburn Professional Products Division.

Presented above, from left to right, top to bottom are:

Binkhorst Irido-Capsular (2-Loop).
Designed by Dr. C.D. Binkhorst.

Binkhorst Iris Clip (4-Loop).
Designed by Dr. C.D. Binkhorst.

Rayner Choyce Mark VIII Anterior Chamber Implant.
Designed by Mr. D. Peter Choyce.

Rayner Choyce Mark IX Anterior Chamber Implant.
Designed by Mr. D. Peter Choyce.

Fedorov II 'Sputnik.'
Designed by Dr. S.N. Fedorov.

Fedorov Type I (Iris Clip).
Designed by Dr. S.N. Fedorov and Dr. C.D. Binkhorst.

All of the lenses are available for immediate delivery to registered investigators.

To order, or for further information, call toll free (800) 237-5906. In Florida call collect (813) 443-2606.

Prospective Investigators: Please write Coburn Professional Products, Regulatory Affairs Dept., 1375 South Fort Harrison, Clearwater, FL 33516.

Exclusive Distributors:

COBURN
Professional Products Division

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What's 3M doing with our lenses?

Building confidence into IMPLENS® intraocular lenses.

Backed by 3M's research capabilities and technological expertise, we've developed consistent quality lenses...guaranteed superior optics...and immediate availability.

Innovative quality control measures yield impressive results. Each lens we produce is certified to be within the specification tolerance of ±.25 diopters of the labeled power and 74% of theoretical maximum resolution. In an independent university study of 10 randomly selected IMPLENS lenses*, resolution efficiency averaged 85.0% ±4.2%, and dioptric power accuracy ranged from 0 to ±.18 D—well within specification tolerance. Edges are rounded and polished to the same exacting smoothness as the optic surface. Only McGhan lenses have molded polypropylene posterior loops which ensure a permanent consistent angle to prevent pinching and minimize iris chafing.

McGhan—now a 3M subsidiary—has advanced to the forefront of intraocular lens manufacturers. Research projects include the development of improved lens styles and new protective lens coatings. We offer a complete selection of intraocular lens designs, most in full dioptric range from 14 to 25 in 1/2 diopter increments... delivered rapidly to meet surgery schedules.

See for yourself what 3M is doing with our lenses. Call one of the toll-free numbers below, today.

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700 Ward Drive
Santa Barbara, CA 93111
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Ordering Information: (800) 235-6911
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Focused on the present to envision the future

*Data on file, McGhan Medical Corporation.
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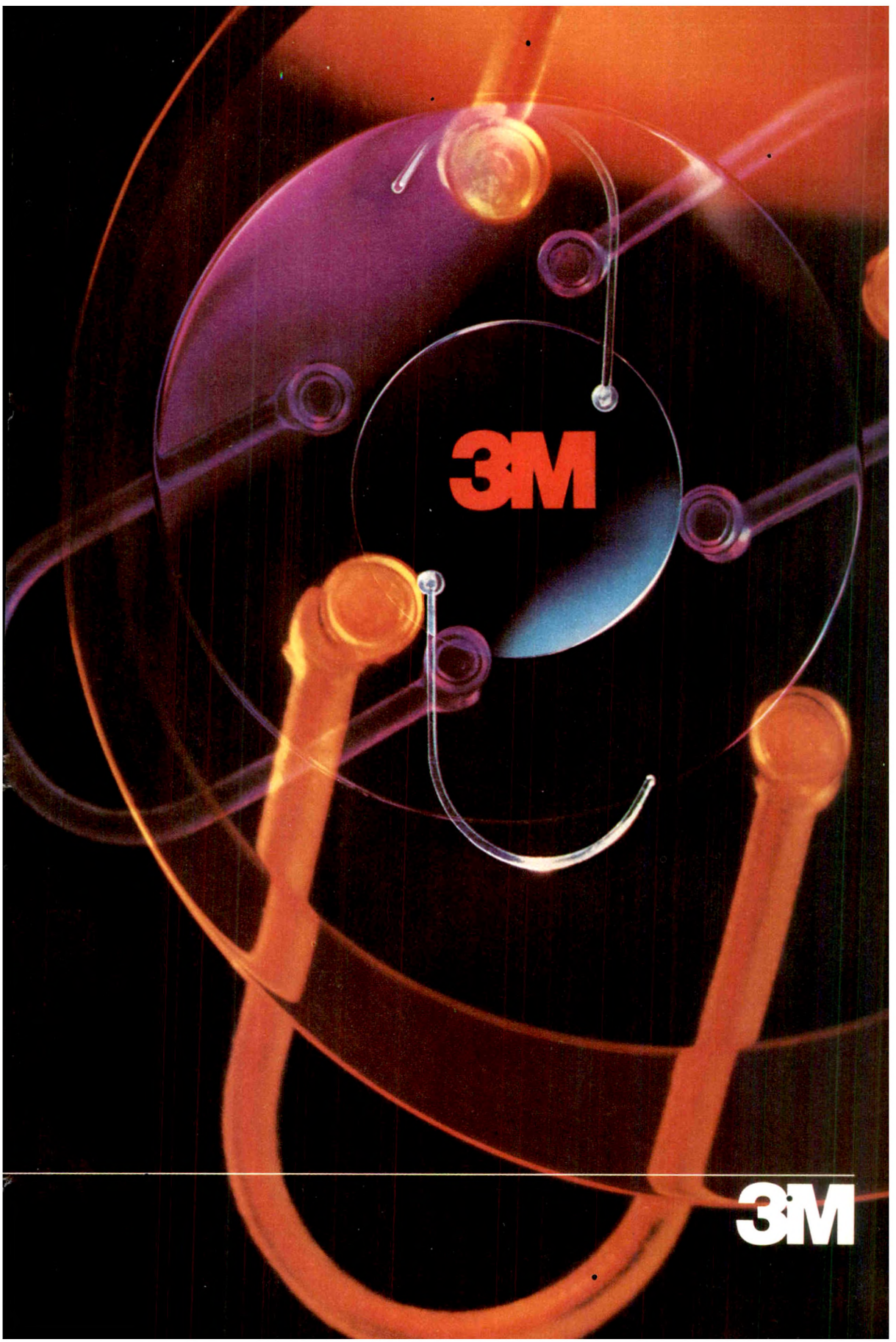
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POLYCON®

(silafocon A) CONTACT LENS

Provides visual acuity, maintains normal corneal physiology

The POLYCON lens* is a rigid, oxygen-permeable contact lens with excellent stability. It is made from a copolymer containing silicon and methyl methacrylate (MMA).

Extensive clinical data demonstrate distinct benefits

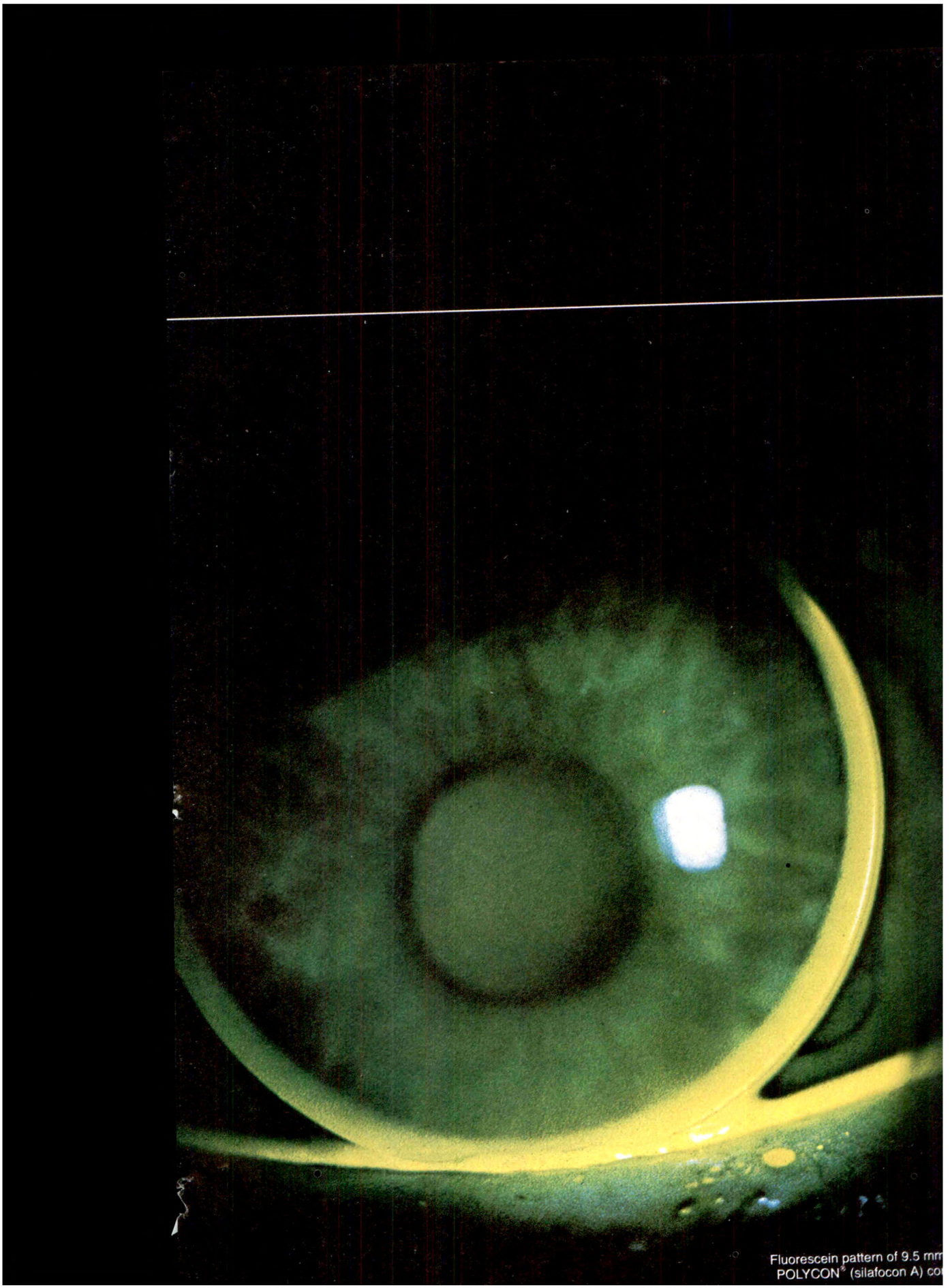
418 patients completed a multiclinic study** with the following results:

No edema reported in 96.4% of patient visits
No spectacle blur reported in 99.5% of patient visits
No flare or halo problems reported in 99% of patient visits
All-day comfort reported in 90% of patient visits

For more information, call toll-free (800) 528-0366 today; in Arizona, call collect (602) 242-6146.

Please see the third page of this advertisement for brief summary information.
**Data on file, Syntex Ophthalmics, Inc.

SYNTEX
SYNTEX OPHTHALMICS, INC.



Fluorescein pattern of 9.5 mm
POLYCON® (silafocon A) co

POLYCON®
(silafocon A) CONTACT LENS

BRIEF SUMMARY

INDICATIONS
The POLYCON contact lens is indicated for the correction of visual acuity for persons with nondiseased eyes having ametropias, including those with high degrees of corneal or refractive astigmatism, as well as aphakia.

CONTRAINDICATIONS
Acute and subacute inflammations of the anterior segment of the eye; any eye disease which affects the cornea or conjunctiva; insufficiency of lacrimal secretion; corneal hyposthesia, or any systemic disease which may affect the eye or be exacerbated by wearing contact lenses.

WARNINGS
Abrasions and Infections: If the lens becomes less comfortable to the wearer than when first placed on the wearer's cornea, a foreign body may be present. The patient should remove the lens immediately. If discomfort persists, an eye care practitioner should examine the patient as soon as possible to determine if any corneal abrasion, ulceration, irritation or infection is present.

Aphakic Patients: Aphakic patients should not be fitted during the postoperative period until the surgeon determines that the eye has healed completely.

Lens Care Regimen: Only use Preflex® Sterile Cleaning Solution, Normol® Sterile Solution, and Adapettes® Sterile Lubricating Solution with the POLYCON lens. Store ONLY in Normol® Sterile Solution. Patients must adhere to recommended daily lens care regimen. FAILURE TO DO SO MAY RESULT IN DEVELOPMENT OF SERIOUS OCULAR INFECTIONS.

Medicaments and Eye Drops: Wearers must not use any medicaments or ophthalmic solutions other than Adapettes solution prior to inserting the lens or while the lens is on the eye.

Wearing Restrictions: Remove before sleeping or in the presence of noxious and irritating vapors.

PRECAUTIONS
CLEANING AND DISINFECTION
THE **POLYCON** CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER.

To disinfect the lens, it is stored in fresh Normol solution for a minimum of four hours daily in the patient lens storage case.

After removal of the lens from the storage case, it is rinsed thoroughly with Normol solution. Adapettes lubricating solution is applied to the lens surfaces as a wetting agent prior to inserting the lens in the eye.

ADVERSE REACTIONS
Rainbows or halos around objects or blurring of the vision. Excessive tearing, unusual eye secretions and photophobia.

FITTING AND WEARING SCHEDULE
Conventional methods of fitting contact lenses apply to the POLYCON contact lens.

NOTE: STUDIES HAVE NOT BEEN PERFORMED TO SUPPORT SAFETY OF THIS LENS FOR LONGER THAN THE RECOMMENDED WEARING TIME.

A POLYCON Contact Lens Patient Care Kit must be provided at the dispensing visit.

Preflex, Normol and Adapettes are trademarks of Burton, Parsons & Company, Inc.

SYNTEX
SYNTEX OPHTHALMICS, INC.
PHOENIX, ARIZONA 85015

Announcement of the
Twentieth Annual Instructional Course
In Contact Lens Fitting
Friday and Saturday, March 28-29, 1980
NEW ORLEANS
Sponsored by
The Rudolph Ellender Medical Foundation
In conjunction with
The Louisiana State University Eye Center
Endorsed by
The Contact Lens Association
Of Ophthalmologists
A.M.A. —Approved as
Continuing Medical Education Program
(Sixteen Hours Credit in Category I)

PLACE: Fairmont Hotel, New Orleans

TUITION: $225.00 (Please make check payable to Rudolph Ellender Med. Fd. Mail to 136 S. Roman, New Orleans 70112 U.S.A.)

FACULTY:
JOS. A. BALDONE, M.D., New Orleans
OLIVER H. DABEZIES, JR., M.D. New Orleans
MILES H. FRIEDLANDER, M.D., New Orleans
RICHARD J. HESSE, M.D., New Orleans
FRANK B. HOEFLE, M.D., New York City
BREIN HOLDEN, PH.D., Kensington, Australia
GEORGE H. JONES, M.D., Baton Rouge
HERBERT E. KAUFMAN, M.D., New Orleans
DAVID M. METZNER, M.D., New Orleans
WHITNEY G. SAMPSON, M.D., Houston, Texas
EDWARD L. SHAW, M.D., Phoenix, Arizona
TOM F. SPRING, M.D., Kew, Australia
LOUIS A. WILSON, M.D., Atlanta, Georgia

TOPICS: Conventional hard and soft contact lenses, and extended wear contact lenses.

Pre-Course Basic Lectures: 4 hours on the basics of hard and soft contact lens fittings on Thursday afternoon, March 27, 1980—Additional tuition $50.00

Basic Lectures: By Industry—no additional fee, Friday and Saturday evenings, March 28-29, 1980.

Post-Course Modification Seminar: Sunday, March 30, 1980—8:00 a.m. 'til 12 noon—Hard Lens Modification Course with audience participation—Limit 36 Persons—Additional tuition $50.00

FOR FURTHER INFORMATION CONTACT:

Jos. A. Baldone, M.D.
L.S.U. EYE CENTER
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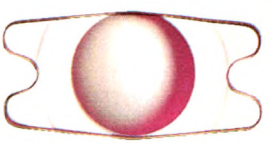
LADIES DAY ACTIVITIES:
Usually French Quarter and Garden District Tour

Only PC produces all three of these anterior chamber intraocular lenses

KELMAN II™



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PRECISION OPHTHALMIC LENSES IN THE EYE • ON THE EYE 40 1939-1979

Caution: Intraocular lenses are an investigational device limited by Federal law to investigational use. Federal law restricts this device to sales by or on the order of a physician.

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Unisol™
Preserva
Saline So
For rinsing anc
of hydrophilic
Contains no p
25 -day supply
Contains 25 d
coc
Unisol™
DIRECTIONS:
Use one bottle of Unisol™ to fill your carrying case and to rinse cleaner from your lenses prior to heat disinfection. Lenses are ready to wear without addition-al rinsing following heat disin-fection. If your heating unit is not available, lenses may be disinfected by immersing your lenses in Unisol™ in your carry-ing case and dropping the seal-ed case into a pan of boiling water. Remove the pan from the heat after 10 minutes and allow the water to cool before removing your lenses.
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STERILE
Unisol™
Preservative-free
Saline Solution
For rinsing and heat disinfection
of hydrophilic (soft) contact lenses.
Contains no preservatives.
10 -day supply
Contains 10 disposable 1/2 fl. oz. (15ml) bottles.
cooperVision
10 Unisol™
Saline Solution
Preservative-free

NOW YOU CAN ELIMINATE A MAJOR CAUSE OF EYE IRRITATION AMONG SOFT LENS WEARERS.

Preserved saline has been used for soft lens disinfection to avoid the problems that sometimes result from misuse of salt tablets—saline contamination and eye infection.

Preserved saline eliminates possible contamination, but it introduces yet another major problem: ocular sensitization and allergic reaction to thimerosal.

Studies have shown that thimerosal may cause eye irritation in up to 50% of all soft lens patients.[1] Furthermore, this irritation appears to increase over time, so that patients who initially experience no discomfort may eventually become sensitive to thimerosal after repeated use.[2] Since all existing premixed saline solutions for soft lens care are preserved with thimerosal, soft lens patients are left with no alternative but to risk eye irritation.

But now this major cause of eye irritation can be eliminated—with Unisol,™ the sterile saline solution packaged in single-dose vials. Unisol™ contains no preservatives, so it eliminates the risk of preservative-induced irritation.

In clinical studies[3] with patients who had previously experienced eye irritation from preserved saline, Unisol™ was shown to greatly reduce or eliminate symptoms of this irritation.

Unisol™ also fosters better patient lens care, because it offers the sterility and convenience of premixed saline. And patients find the compact size of each 15-ml vial makes Unisol™ easy to handle, carry, and store.

Unisol™ offers all of these patient benefits—at an average daily cost comparable to existing preserved-saline products.

So why have your soft lens patients risk eye irritation problems caused by preserved saline? Now there's a simple solution: Unisol,™ preservative-free saline.

[1] Suzuki H: Allergic conjunctivitis and blepharoconjunctivitis caused by thimerosal (preservative). Japanese Journal of Clinical Ophthalmology 26: 7-12 (1972).

[2] Gasson A: Aftercare problems relating to lens handling and disinfection. The Contact Lens Journal 7: (5) 40-44 (September 1979).

[3] Yamane SJ: Studies with a unit dose saline solution. Contact Lens Forum 4: 91-95 (August 1979).

SMITH, MILLER & PATCH
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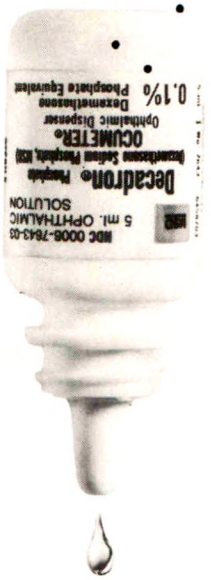
UNISOL™
Preservative-free Saline Solution

For steroid-responsive inflammatory disorders of the anterior segment

CONVENIENCE... drop after drop



Sterile Ophthalmic Solution

DECADRON® Phosphate

(DEXAMETHASONE SODIUM PHOSPHATE | MSD)

0.1% Dexamethasone Phosphate Equivalent

IN THE OCUMETER®

OPHTHALMIC DISPENSER

a highly effective medication

- The OCUMETER conveniently dispenses one drop at a time
- No eyedropper is necessary
- Remains stable at room temperature
- May be carried in pocket or purse
- pH compatible with that of the eye

℞

On your prescription, be sure to include the word "OCUMETER."

Contraindications: Acute superficial herpes simplex keratitis.

Fungal diseases of ocular or auricular structures.

Vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva.

Tuberculosis of the eye.

Hypersensitivity to a component of this medication.

Perforation of a drum membrane.

Warnings: Employment of steroid medication in the treatment of stromal herpes simplex requires great caution; frequent slit-lamp microscopy is mandatory.

Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from pathogens liberated from ocular tissues.

In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids.

Acute purulent untreated infection of the eye or ear may be masked or activity enhanced by the presence of steroid medication.

Usage in Pregnancy—Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated.

Precautions: As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.

Intraocular pressure should be checked frequently.

Adverse Reactions: Glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex liberated from ocular tissues, perforation of the globe.

Rarely, filtering blebs have been reported when topical steroids have been used following cataract surgery.

Viral and fungal infections of the cornea may be exacerbated by the application of steroids.

Rarely, stinging or burning may occur.

How Supplied: Sterile ophthalmic solution in 2.5-ml and 5-ml glass bottles with dropper assembly and in 5-ml OCUMETER® ophthalmic dispensers, containing per milliliter of buffered solution: dexamethasone sodium phosphate equivalent to 1 mg (0.1%) dexamethasone phosphate; creatinine, sodium citrate, sodium borate, polysorbate 80, disodium edetate in the OCUMETER, sodium hydroxide to adjust pH in glass bottles, hydrochloric acid to adjust pH in plastic dispensers, water for injection, and sodium bisulfite, phenylethanol, and benzalkonium chloride added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

J7D001(009)

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The 500 Series of

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for Retinal Detachment Surg

A new line of silicone sponge expl by Medical Instrument Rese Associates, Inc.

- Available in standard 3 m 4 mm, and 5 mm cylinde and a 5.5 mm x 7.5 mm ov

PLUS

- Two new shapes . . .
  - Frederick Design, a 4 mm x 12 mm rectangle for large retinal tears or multiple breaks
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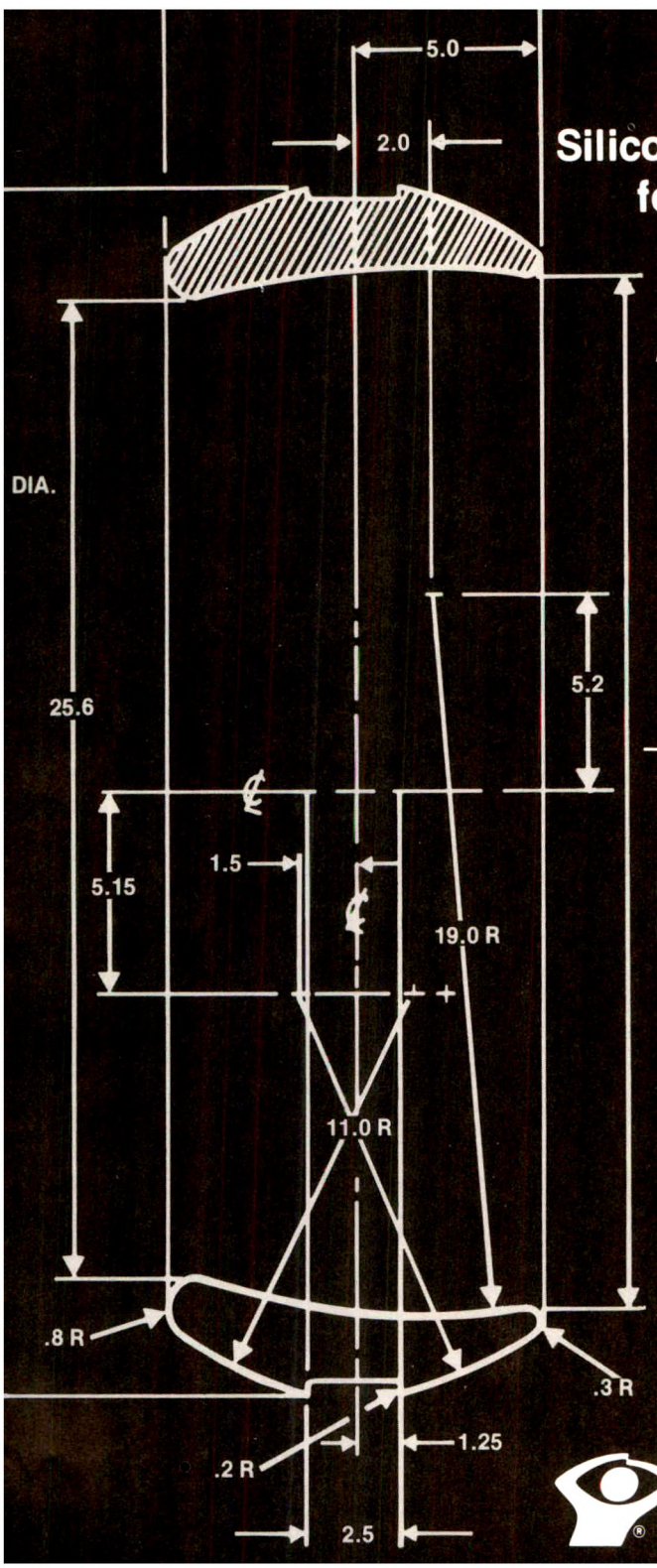

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ANATOMICAL TIRE™

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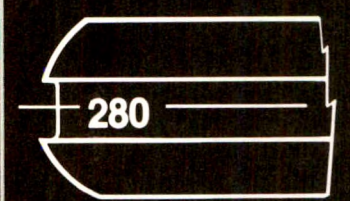
- All tires standardized to wider anatomical diameter
- 360° buckling with any single tire



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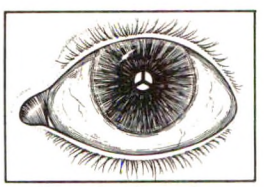
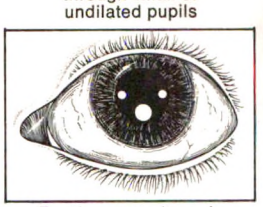
Our Small Pupil Feature has been Copied But Never Equaled

UNIQUELY OPTIMIZED SCHEPENS-POMERANTZEFF OPHTHALMOSCOPE

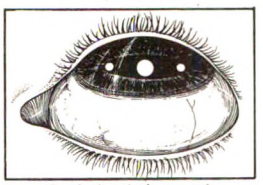
Provides best stereoscopic view of fundus in every clinical case



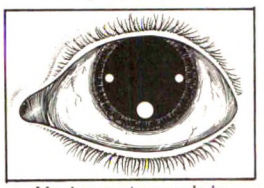
Binocular observation through small or undilated pupils



Routine posterior pole observation through dilated pupils



Optimized view and illumination of fundus periphery



Maximum stereopsis in widely dilated pupils. Better vision around opacities in transparent media

COMFORTABLE improved headband with soft, thick foam pads

EASY TO USE built in convergence . . . no accommodation required . . . precision optics

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Result of
20 Years of
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- High Frequency 13.56 MHz power minimizing scleral damage
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- Pending U.L. approval Specification #544

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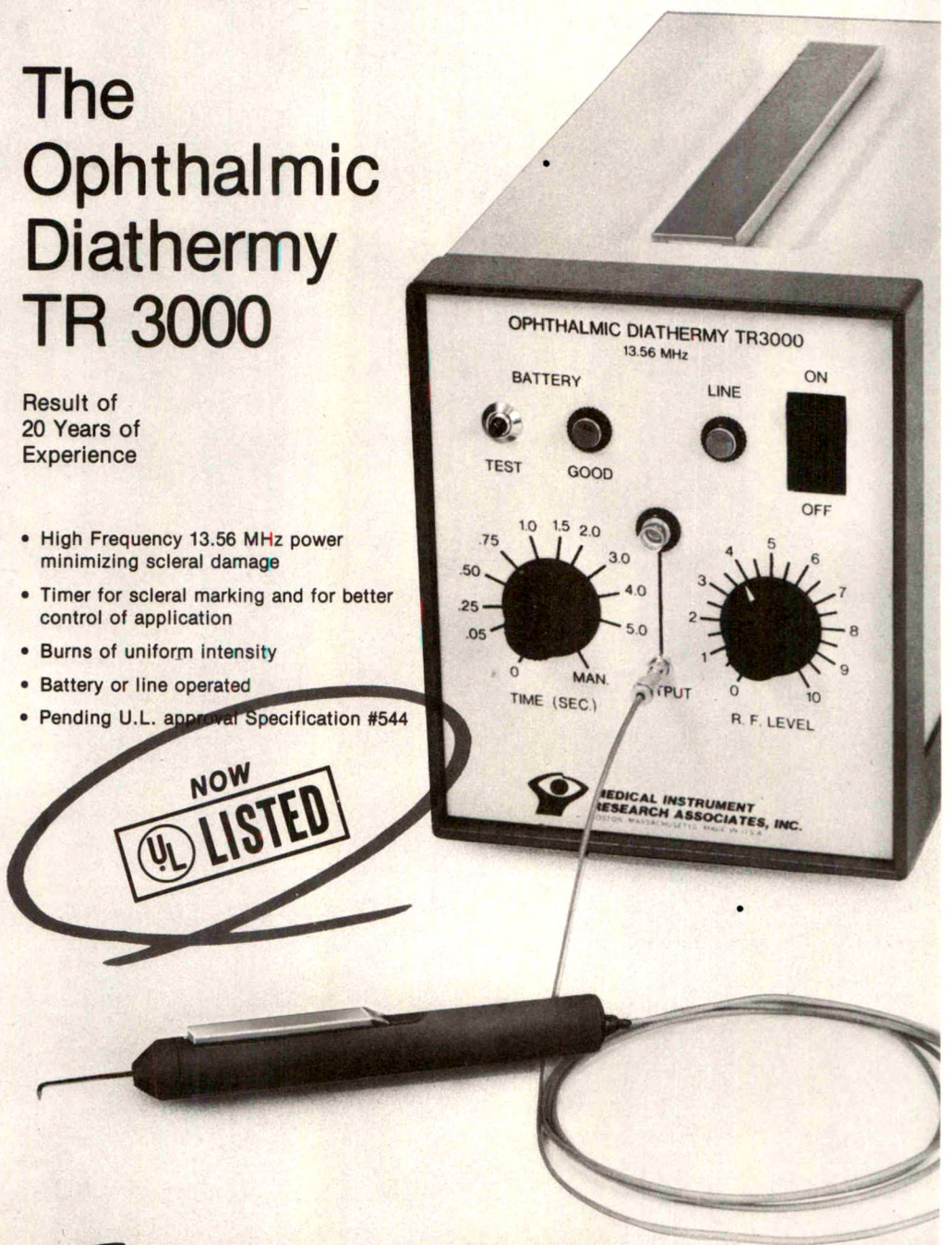

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rynco scientific corporation

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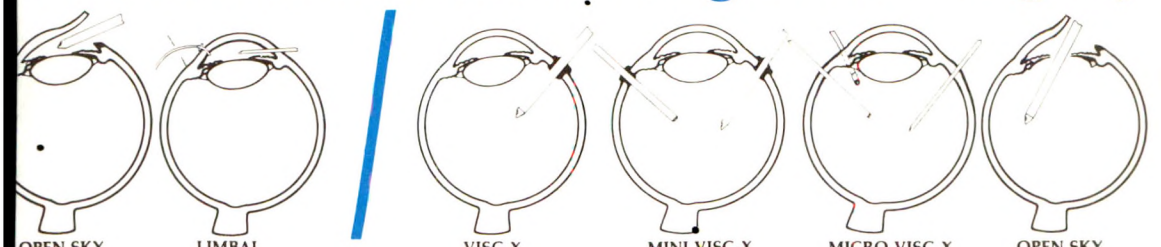
*U.S. Patent No. 3900250, Semi-rigid Gas Permeable Contact Lens

Anterior or Posterior Segment Surgery



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Your choice
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of tip sizes

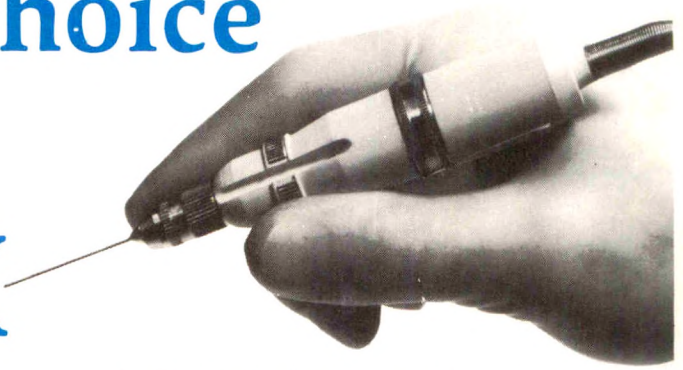
VISC-X
1 Port System
1.65 or 2.3 mm

MINI VISC-X
2 Port System
1.65 mm

MICRO VISC-X
3 Port System
1 mm

OPEN SKY
Your choice
of tip sizes

It's your choice with the VISC-X



Automatic or Manual Suction/Reflux
Micro-Tips: 1 mm
Mini-Tips: 1.65 mm
Lentectomy Tips: 2.3 mm

The VISC-X is a revolutionary new concept in systems for anterior-posterior segment surgery. It permits the surgeon to employ a wide variety of techniques through singular or multiple incisions. Using the modular building block approach, the surgeon can create a system customized for present requirements and preferences. As needs change, the VISC-X systems may be expanded to permit additional techniques and procedures.

Your Choice...

Oscillating, forward, reverse cutting modes - variable to 1,080 cuts per minute.

Independent or concurrent cutting, suction, reflux, illumination, and bipolar bimanual diathermy

Exceptionally bright fiber optics. Variable illumination, coaxial or separate, hooked or straight, with or without infusion. Bright enough for intraocular video display, tapes and films.

Hand held quartz infusion or quartz floating contact lenses.

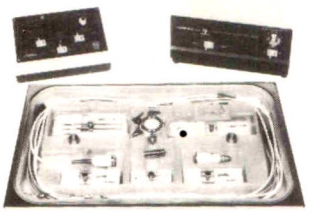
Wide choice of probes, cannulas, infusion ports and plugs.

1, 2, or 3 port systems for uni or bimanual techniques

Hooked or straight needles and pics, with or without infusion, for all procedures.

Automatic suction/reflux achieves instantaneous pressure equilibrium within the eye. Manual suction if desired.

The VISC-X is lightweight and modular - assembles in seconds without tools. Rechargeable battery operation for patient safety. Surgery is aided greatly by use of special double lip, self-sharpening cutting tips which exert no traction on tissue or vitreous.



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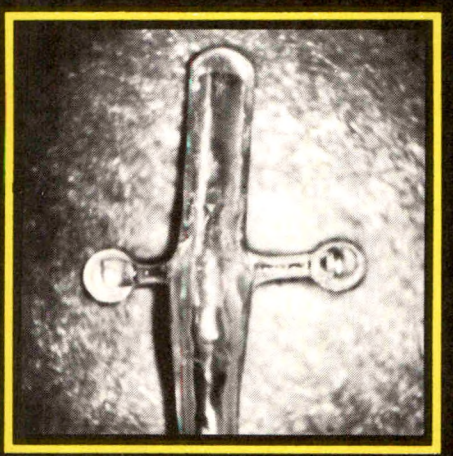

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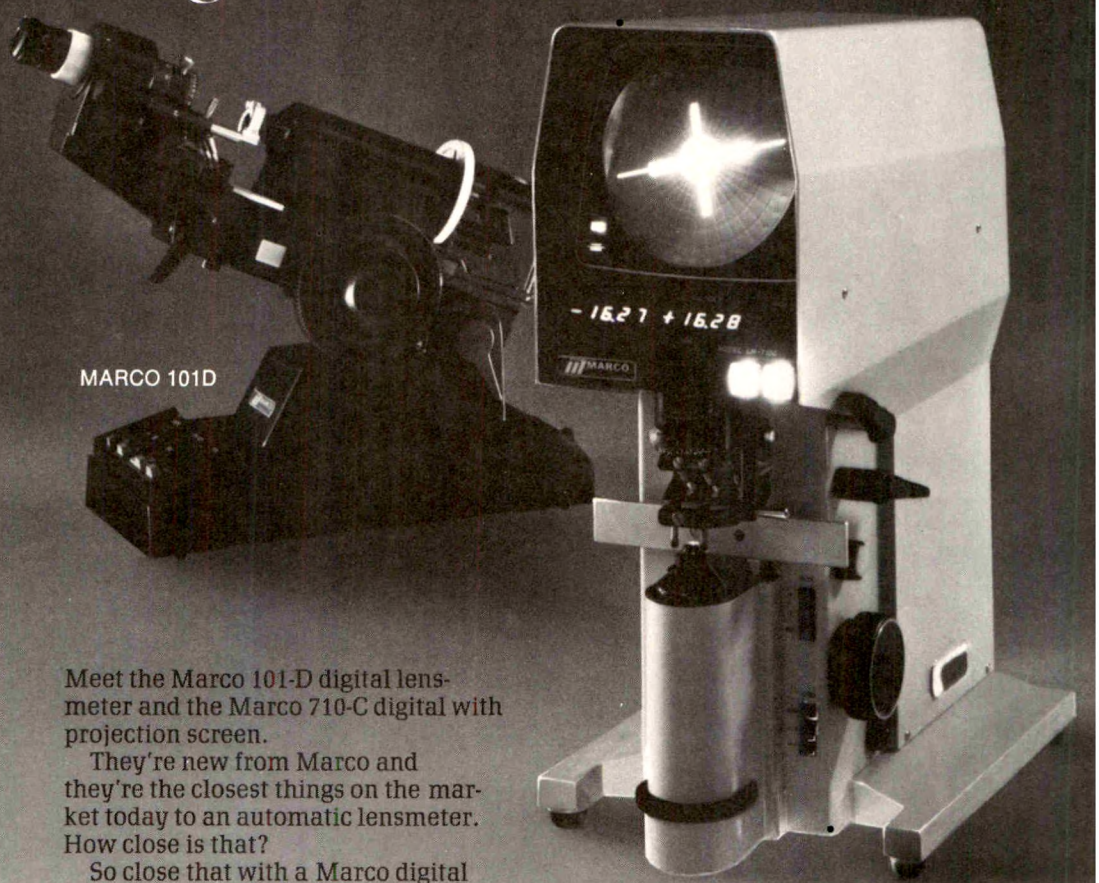

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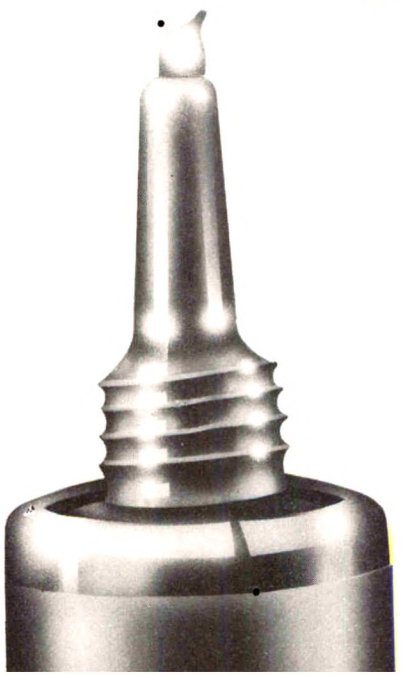

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* Luxenberg, M.N., and Greek, K.: Reduction of Corneal Edema with topical hypertonic agents. Am. J. Ophth. 71:847, 1971.

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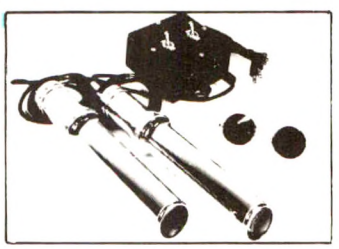

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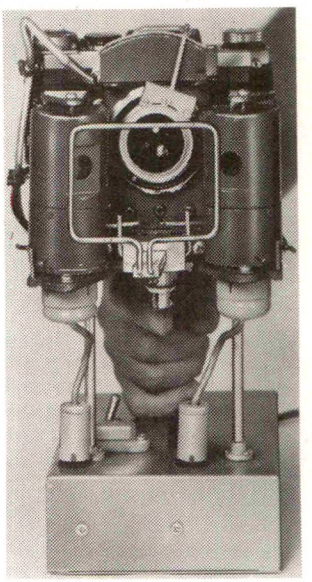

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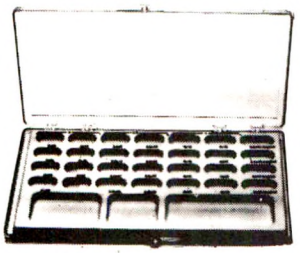

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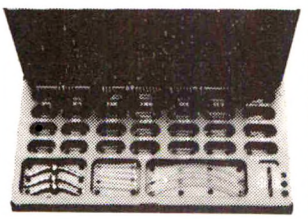

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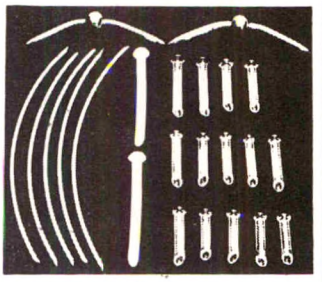

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* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
L.T. Jones M.D. and J.L. Wobig M.D., Surgery of the Eyelids and Lacrimal System, Aesculapius Publishing Company, 1976.

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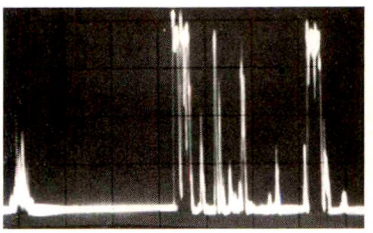
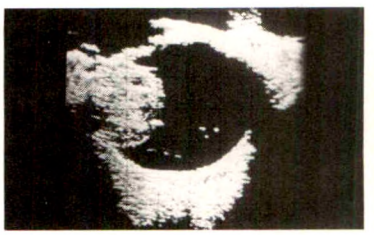
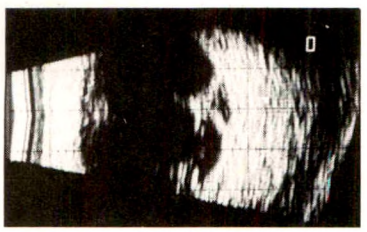


1. *A-scan* of tumor of the ciliary body showing attenuation pattern of a malignant melanoma.



2. Immersion *B-scan* of the same melanoma with posterior vitreous hemorrhage.



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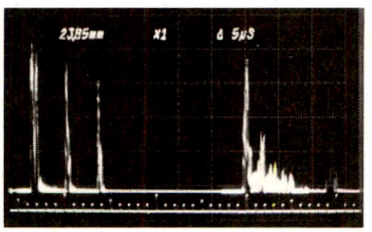

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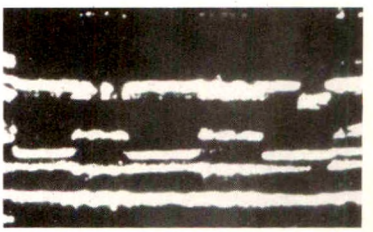

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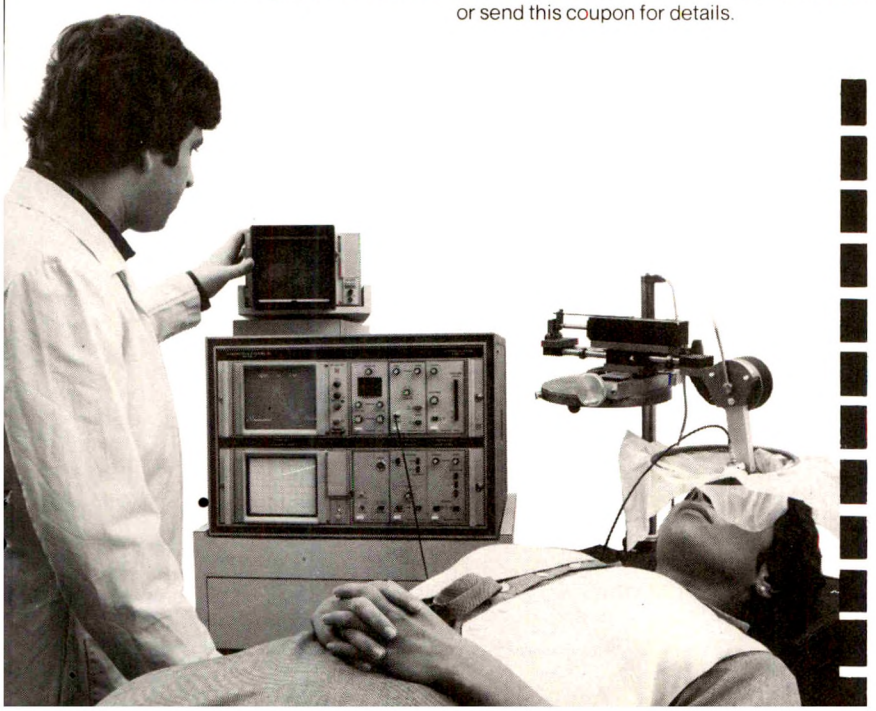

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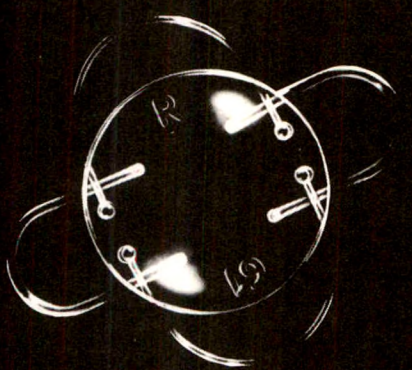

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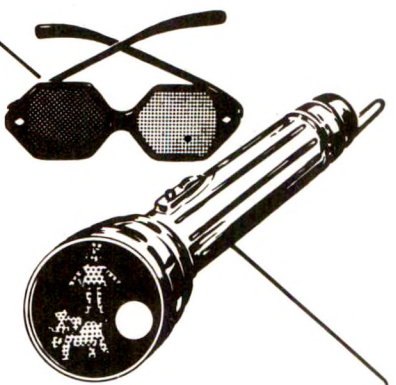

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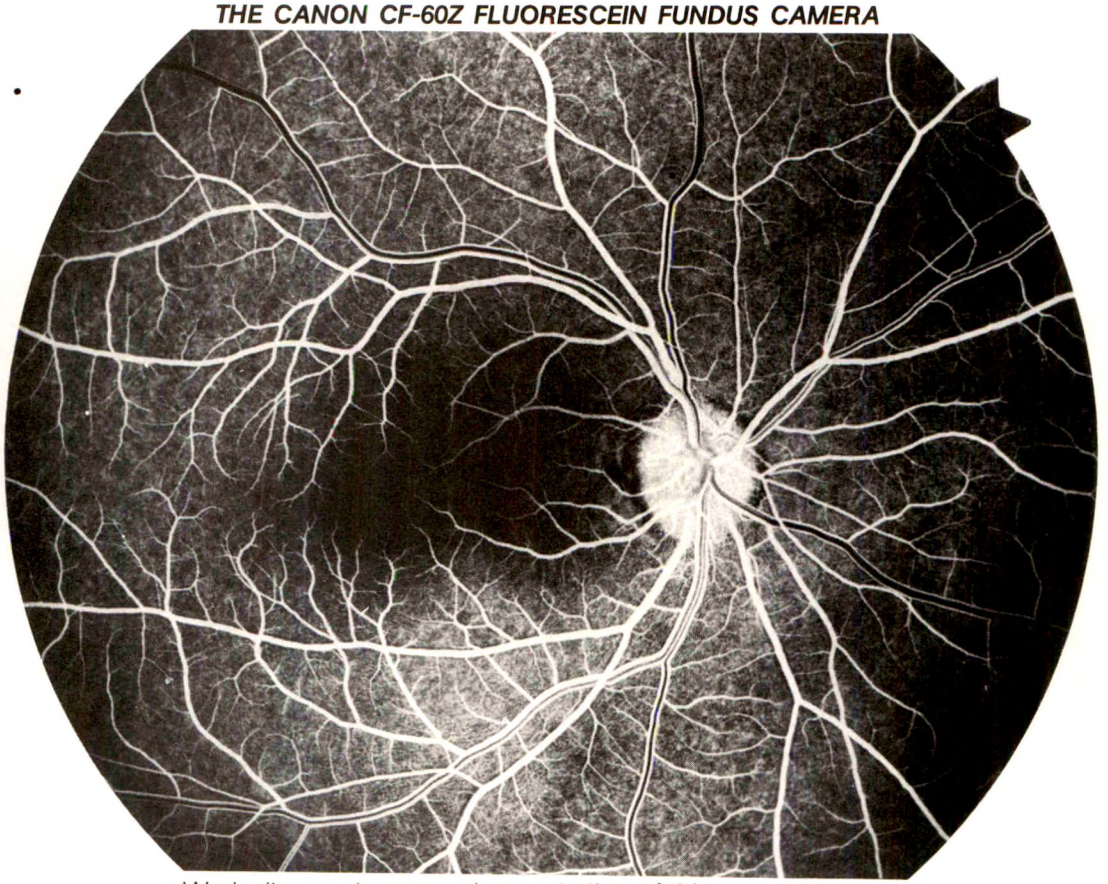

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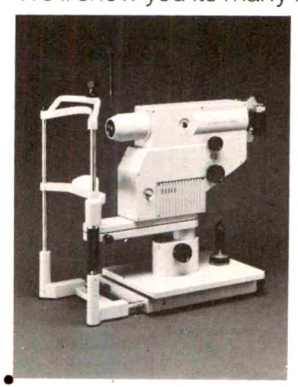

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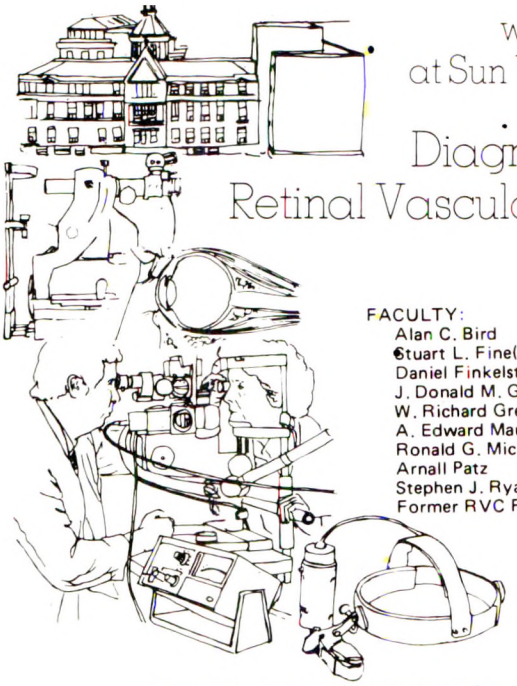

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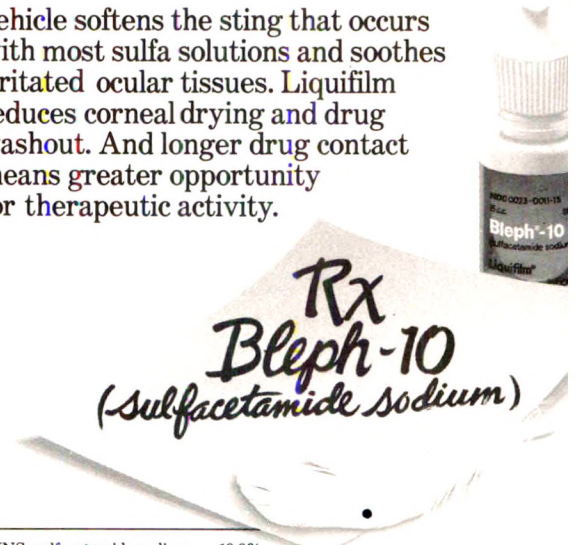

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AMERICAN JOURNAL OF OPHTHALMOLOGY™
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THE CORRECTION OF APHAKIA

XXXVI Edward Jackson Memorial Lecture

Herbert E. Kaufman, M.D.
New Orleans, Louisiana

Edward Jackson was born in 1856 and died in 1942. He was a giant in our field—the founder of the American Board of Ophthalmology, and the founder and first editor of the third series of The American Journal of Ophthalmology. He was also a researcher and a teacher with a primary interest in optics. Although he is best known for his role in developing the cross-cylinder technique for refraction of astigmatism, he also had a deep interest in aphakia. Only once in the 35 years that the Edward Jackson Memorial Lecture has been given has the topic been confined primarily to optical problems, in 1958, when A. Linksz spoke on aniseikonia. I do not believe my own knowledge of optics is exceptional; however, I will discuss a subject that would have fascinated Jackson, the correction of aphakia in general, and more specifically, the surgical correction of aphakia.

From the Lions Eye Research Laboratories, Louisiana State University Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana.

This study was supported in part by Public Health Service Grants EYO2580 and EYO2377 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland; and an unrestricted grant from Research to Prevent Blindness, Inc. Presented before the 84th annual meeting of the American Academy of Ophthalmology, San Francisco, California, Nov. 5, 1979.

Reprint requests to Herbert E. Kaufman, M.D., Louisiana State University Eye Center, 136 S. Roman St., New Orleans, LA 70112.

Spectacle Correction of Aphakia

Although spectacles have been used for many years as the standard correction for aphakia, there is much interest in contact lenses and intraocular lenses, as well as other treatment modalities, because the correction obtained with aphakic spectacles is far from ideal. The world is seen at a magnification of 25 to 35% and it is distorted in the periphery. Lines are bent and continually change shape as the spectacle wearer moves, causing his visual world to shimmer and appear unbalanced. The peripheral visual field is obliterated in a moving ring scotoma and objects appear to pop in and out of the field. The lenses distort the places of objects in space and because of the magnification effect, spectacles generally cannot be used in monocular aphakic individuals. Although such spectacles have been improved, problems remain.

Prolonged-Wear Contact Lenses

Prolonged-wear contact lenses offer an alternative to spectacles, but they require continual care over a period of years, replacement of lenses, and considerable continuing expense and trouble for the patient.[1] The incidence of allergies, intolerance, and long-term complications is unknown. At a recent National Eye Institute Conference on Aphakia, it was estimated that only approximately one half of the patients who are aphakic would be

able to wear prolonged-wear lenses for a period of more than five years, even though the immediate results may seem much more encouraging. Progress has been great in the area of contact lenses, but they do not as yet provide the complete solution to the problems of aphakia.

Intraocular Lenses and the Corneal Endothelium

Intraocular lenses have opened a new world for the aphakic patient. However, a variety of complications are associated with intraocular lenses. These include the uveitis-glaucoma-hyphema syndrome,[2] which may be avoided by proper manufacturing techniques and newer lens designs; sterile hypopyon, which also seems to be connected with manufacture and sterilization; retinal detachments, which may be more difficult to correct but usually can be successfully managed; and an increased incidence of corneal edema.

We have been particularly interested in the problem of endothelial damage and corneal edema and have approached it from several points of view. Research on the corneal endothelium in our laboratories began with the studies of Bourne and Kaufman[3] in which two major observations of great clinical importance were made. First, we confirmed what had been suspected but never documented, that human endothelial cells seem not to divide at all, or divide seldomly. We also saw that endothelial cells are lost continually with age, and that all endothelial healing seems to occur by the spreading and enlarging of the remaining cells. Two other factors became apparent. First, if enough cells are lost, corneal edema will occur and both the initial cell count and cell loss at surgery become critical. Second, sufficient cell loss at surgery may result in a clear cornea that later decompensates as additional cell loss occurs with age. This understanding of the biology of the human endothelium proved to be central to all of our later work.

The next studies[4,5] we did on patients with intraocular lenses showed that considerable cell loss occurred during insertion of the intraocular lens. This was confirmed in studies of patients with intraocular lenses that were done by a number of skillful surgeons.[6–8] It was further amplified by work that clearly correlated the surgeon's estimate of endothelial trauma, especially in terms of lens-endothelium contact, with the loss of cells observed by specular microscopy.[9–11] Finally, in our laboratory, we discovered that touch between the endothelium and the intraocular lens caused endothelial cells to adhere to the lens surface, which could result in profound endothelial damage.[12]

The first result of the acceptance of these studies was the understanding that if contact between endothelium and lens could be avoided, endothelial cell loss could be prevented.

Surgeons making a deliberate attempt to avoid even momentary contact observed substantially less cell loss than had been seen in older series in which brief contact was not thought to be important. Avoiding endothelium-lens contact prevented mainly the loss of corneal endothelial cells.[9,11–14] Our studies, therefore, resulted in a general modification of surgical technique and with it improved safety for the patient.

The second approach to the prevention of endothelial cell damage was the search for coatings that could change the nature of the intraocular lens surface so that damage resulting from cell contact with methacrylate or glass could be avoided. Originally, we showed that imperfect, sticky coatings of hydroxyethylmethacrylate and polyvinyl pyrrolidone could reduce cell loss.[12] This has been confirmed by others.[15] Our finding that hydroxyethylmethacrylate soft lens mate-

rial did not cause endothelial damage has also been confirmed by Levy, Roth, and Gangitano.[16] Some investigators have used mucin to coat the lens,[17] others[18] have tried hyaluronic acid. A commercial coating is being tested,[19] and other coating substances are being developed to give the surgeon a margin of safety even if endothelium-lens contact occurs.

This phenomenon of damaging surface adhesion is probably important in areas of medicine other than ophthalmology.[20,21] Such surface adhesion is thought to contribute to abdominal adhesions, as rubber gloves damage the peritoneum. It may also contribute to tracheal damage from cannulae and, therefore, to tracheal susceptibility to infection. Other types of catheters also seem to cause previously unsuspected damage by this same mechanism, so it may be that our initial studies of the corneal endothelium will prove to be of some benefit to medicine in general.

A third approach to the problem of endothelial damage has not often been considered. This concept depends on the biology of human corneal endothelium itself. These cells are relatively unique in their apparent inability to multiply. The corneal endothelium of most animal species multiplies readily if its cells are injured. In tissue culture, human endothelium is capable of multiplying if given the necessary additive factors. Possibly the missing factors that would stimulate endothelial multiplication could be relatively simple, and perhaps could be provided to the cells.

Jumblatt, Maurice, and McCulley[22] showed that, in rabbits, endothelium could be grown in tissue culture and then be used to repopulate corneas lacking endothelial cells. These cells transplanted from culture appeared to function, and the corneas stayed thin and clear.

Gospodarowicz and associates[23,24] have done extensive work to amplify Maurice's concept by using a variety of cells and species, and they have indicated that vascular endothelium from the patient himself might be used to resurface his own cornea, perhaps in this way avoiding rejection problems. Gospodarowicz, Mescher, and Birdwell[25] have also shown that bovine corneal endothelial cells, which normally divide, have their rate of division enhanced by both fibroblast and epidermal growth factor.

Fabricant and associates,[26] studying this problem in our laboratory, showed that human corneal endothelial cells have specific receptors for epidermal growth factor, and indicated that, in general, when such receptors are present, they are biologically active. They have shown further that, in tissue culture, epidermal growth factor facilitates cell division in human endothelium, causing it to grow much more rapidly than it does under other circumstances. An intact human cornea kept alive as an organ culture will, when damaged centrally, heal more rapidly in a solution containing epidermal growth factor (Fig. 1). This third approach to the problem of corneal endothelial cell division, therefore, is to provide the tissue with the factor or factors required for multiplication and healing. We cannot yet, at the end of surgery, inject some growth factor and feel confident that the damage we have done will heal itself, but these experimental approaches may soon help us clinically.

Despite all of this progress, intraocular lenses remain a problem. The results in children, especially neonates, are far from ideal, and there is general agreement that inserting such lenses in young people is unwise and generally contraindicated. The wisdom of inserting intraocular lenses in both eyes of a patient is also uncertain because of the many unpredictable problems that can occur and have occurred in the past. Such double insertions should be considered only with extreme caution; the second lens placement being

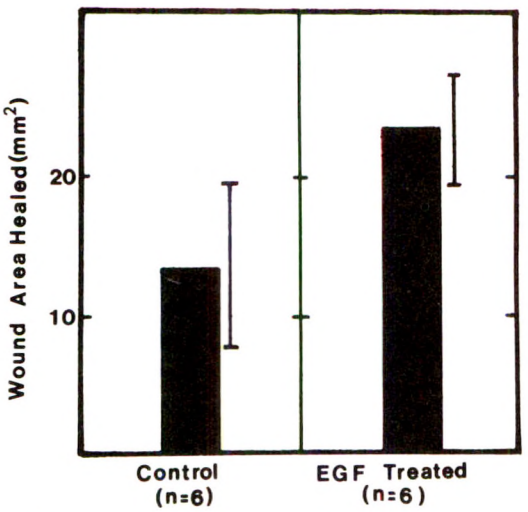

Fig. 1 (Kaufman). Organ cultured human corneas were wounded by freezing a central area 7 mm in diameter. Corneas incubated for 14 days with 20 ng/ml of epidermal growth factor in the medium healed an average of 23 mm², whereas the matched control corneas incubated without epidermal growth factor healed only 13 mm² (P = .01).

performed a significant length of time after surgery in the first eye has proved uneventful and tolerance for the lens seems good.[27] We are still seeing intolerance to the lens plastics, surgical problems, sterile hypopyons, and corneal edema.

Subsequent corneal transplantation can resolve some of the more severe problems resulting from complications of intraocular lens placement if the circumstances warrant. Recently we reported a consecutive series of keratoplasties, some aphakic, others with cataracts removed at the time of surgery (Figs. 2 and 3).[28] With none lost to follow-up and a minimum of one year of observation, we found good visual results and 95% clear grafts, unless the eye had been damaged before the grafting was done (Table). Even this possibility, however, does not mitigate the seriousness of the possible complications associated with intraocular lenses.

Surgical Correction of Aphakia

In continuing our search for an ideal way to provide aphakic correction, we could not ignore the brilliant, pioneering work of Jose Barraquer[29,30] on the modification of corneal shape.

Keratomileusis—Barraquer has shown that, with a microkeratome, it is possible to remove a lamella of cornea that can be frozen and ground to the shape of a positive lens. This lens, if sewn back on the patient's cornea, provides a long-lasting correction for aphakia (Fig. 4).

Keratophakia—Similarly a positive lens can be ground from donor cornea and inserted into the patient's own cornea (Fig. 5). Barraquer has perfected the

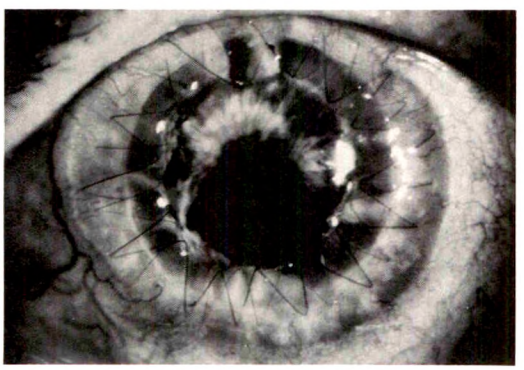

Fig. 2 (Kaufman). Double running suture used in penetrating keratoplasty. Both the 10-0 nylon and 16-μ sutures run in the same direction with no contact between them at any point.

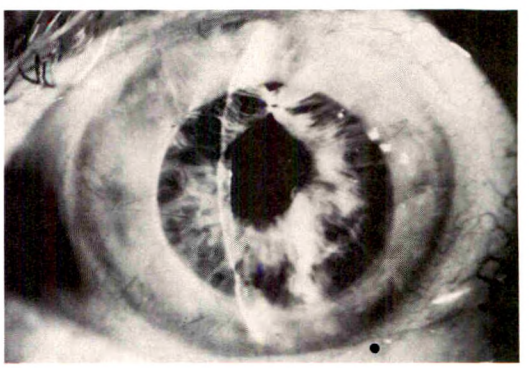

Fig. 3 (Kaufman). The 10-0 suture has been removed and the remaining 16-μ suture may be left in place indefinitely.

TABLE

VISUAL ACUITY AFTER KERATOPLASTY
OR KERATOPLASTY COMBINED WITH INTRACAPSULAR CATARACT EXTRACTION*

Visual Acuity	Aphakic Bullous Keratopathy, % (N=16)	Combined Graft and Cataract Extraction, % (N=17)	Total, % (N=33)
6/24 (20/80) or better	62	94	78
6/12 (20/40) or better	19	88	39

*Prospective, consecutive series with minimum of one-year of follow-up, no dropouts, and 95% clear grafts. Adapted from Olson and associates.[28]

mathematics of this operation, and has developed the complex instrumentation and computer programming necessary to execute it. In his hands, there is no question that excellent visual results can be obtained. The equipment, although expensive, has been simplified to the point where the ophthalmic surgeon can learn to use it, and the calculations have been programmed to facilitate the actual cutting.

The procedure itself, however, is complex; certainly, in the hands of surgeons who seldom use the technique, this kind of surgery is subject to significant complications. First, the surgeon must learn to use the microkeratome and suction ring. Second, he must apply the cornea to the lathe and grind the precise correction, according to the programmed results. In most cases, this is done while the patient is in the operating room. There is always the possibility of the cornea coming off the lathe or of damaging the button. Additionally the difficulties inherent in the physician's learning to do this kind of machine-work and the tremendous cost of the equipment (in its simplest form, now about $50,000) make this technique a hazardous and complex procedure for most good ophthalmic surgeons.

Finally, the exact risk-benefit ratio of such a procedure is not known. Barra-

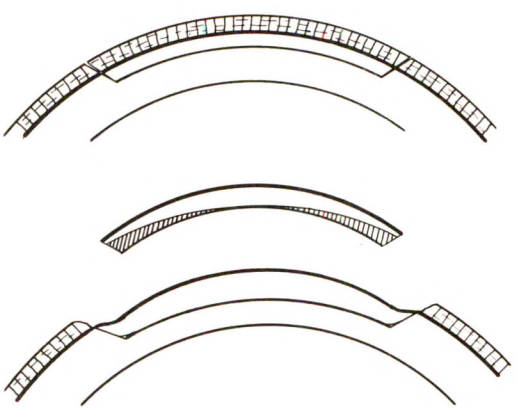

Fig. 4 (Kaufman). In keratomileusis, a lamellar portion of the patient's cornea is removed, frozen, and ground on a lathe to the shape of a positive lens. The cross-hatched area is the tissue removed during grinding. This positive lens is then resutured to the patient's cornea, producing a cornea with a new refractive power.

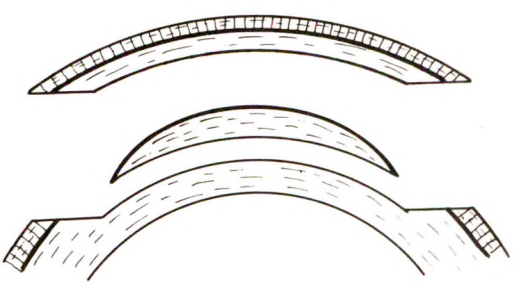

Fig. 5 (Kaufman). In keratophakia, a lamellar portion of the patient's cornea is removed and then sewn back over a button of donor cornea which has been ground to the desired lens power.

quer's results as a whole seem to be excellent, but it is not clear how complete his follow-up is and whether some patients with poor results might be lost to follow-up, thus biasing the series. The correction of aphakia must be a relatively safe procedure, so that the patients need be exposed to the least possible risk. If corneal surface modification is to be used, it must somehow be comparable in risk and benefits to contact lenses and intraocular lenses.

Because Barraquer's ingenious approach seemed to offer real possibilities for the future, we attempted to simplify the technique to make it more practical for use by most ophthalmic surgeons. In our laboratory Larry F. Rich, M.D., showed that these corneas, ground according to Barraquer's newest procedures and using his prescribed solutions, contained only dead cells (unpublished data). The cells were dead, but the matrix of the cornea, its collagen, and its ground substance were preserved, and cells reentered the cornea fairly rapidly, making it a living, vital organ again. Corneas without living cells, however, are easy to preserve. Barraquer originally used silica-dessicated corneas, but found them less transparent than refrigerated corneas frozen on the lathe soon after death.[31] Conversely, we have shown that, once the lenses are ground, they can be kept either frozen or in a glycerine solution, which yields results in both animals and man comparable to those obtained with corneas used immediately.[32]

This implies that corneas could be ground outside the operating room, even by a central facility, and sent to the surgeon on his order. He could then remove the cornea and simply replace it with a preground button. Friedlander[32] has brought together the results of a series using this procedure. We can do a keratophakia or a keratomileusis by ordering a button preground to our specifications, and the only requirement would be to attach the suction ring, apply the microkeratome, and suture on the new, appropriately corrected lamellar graft, or insert the preground lens.

Do the risks and benefits of such a procedure justify its routine use in aphakia? No one knows. The success of this technique for optical correction in children with traumatic cataracts, or in monocular aphakic young people who cannot effectively wear contact lenses, may make it better and safer than other methods of correction, and it may now be the indicated therapy for such conditions. In the case of secondary implantation, keratomileusis, which does not require entering the aphakic eye and thus avoids all the potential complications of vitreous loss, cystoid macular edema, and lens insertion, may well prove to be the preferred choice for safety reasons, particularly in older patients for whom secondary implants might be considered. However, these techniques are still new, and only time will permit us to define its indications precisely. We feel, however, that as the procedure becomes simplified and the risks reduced, the indications will increase.

Surgical Correction of Aphakia: The "Living Contact Lens"

It may be possible to simplify further surgical correction of aphakia, making it still safer for the patient. Could we fashion a lens and put it on top of the cornea as an "epikeratomileusis," or a "living contact lens"? If we could do this, and could leave the central cornea of the patient essentially intact, we would eliminate even the potential hazard of creating the high pressure in the eye that is required for the microkeratome, and the problems associated with using the microkeratome to cut off anterior cornea.

In our laboratory, T. P. Werblin, M.D., first considered this possibility, and we

have proceeded to develop such a technique. Using rabbits, dogs, and monkeys, Drs. Werblin, Friedlander, and I have shown that donor corneal tissue can be frozen and shaped. Epithelium can be removed from the recipient with alcohol, and the preshaped donor disk can be sewn on to a trephine-cut in the recipient cornea that is undermined only in the periphery—off the optical axis. The mark for attachment of the tissue is at approximately 8 mm. Bowman's membrane and the rest of the central cornea are left untouched (Figs. 6-8).

This means that, if the new lens is unsatisfactory, it can be removed without damage to the central cornea of the patient, and the peripheral attachment site would almost certainly not interfere with the patient's vision. It would seem to be easier and safer than anything we now have, even intraocular lenses, but, of course, there are still many questions that must be answered.

First, will the disk attach? The answer to that is "yes."

Second, will the attached disk epithelialize? Again, experimental studies indicate that it will usually epithelialize within a week or two.

Third, will the dead cells of the donor disk be repopulated by living cells from the recipient? This too appears to occur.

Finally, are there any unanticipated risks in the surgery, which now appears nearly risk-free? Will the correction be maintained? Will the interface remain clear and what visual acuities will be achieved? Clearly our work is too recent to be certain of the long-term results; nevertheless, it appears so far that this cornea will behave in the same way as ground, shaped corneas attached to the eye in other ways, and that the correction for aphakia will be long-lasting.

The possibilities of such surgery are exciting. A standard cataract extraction could be done as part of a combined procedure or contact lenses could be tried on patients, and, if for any reason this is unsatisfactory, a "living contact lens"

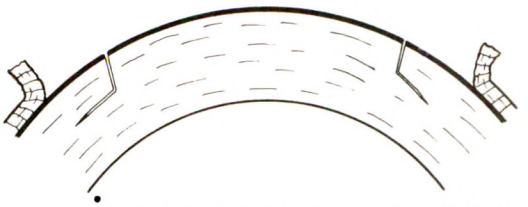

Fig. 7 (Kaufman). The patient's central epithelium is removed by gently rubbing it with a cotton-tip applicator saturated with absolute alcohol, preserving the integrity of Bowman's membrane. Some peripheral epithelium is left untouched. Care must be taken to avoid excessive application of the toxic alcohol. An 8-mm trephine cut is made through the superficial stroma well out of the optical axis. Stroma is undermined slightly along the trephine cut.

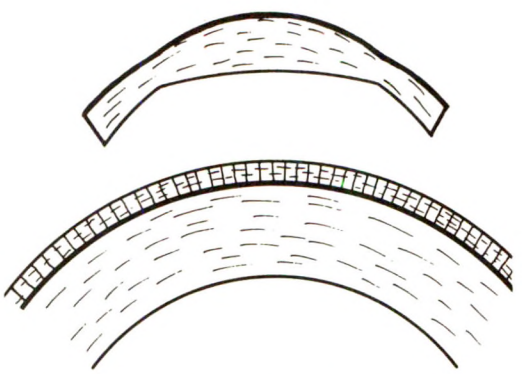

Fig. 6 (Kaufman). In epikeratomileusis, a donor cornea is frozen, ground to the desired lens power with a shape similar to the one in the upper half of the figure, and then stored either in glycerine or in liquid nitrogen.

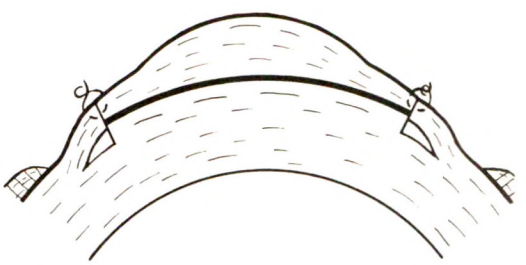

Fig. 8 (Kaufman). The preserved, ground donor tissue is sutured to the patient's cornea over an intact Bowman's membrane. A running suture of 10-0 nylon is used to secure the donor tissue.

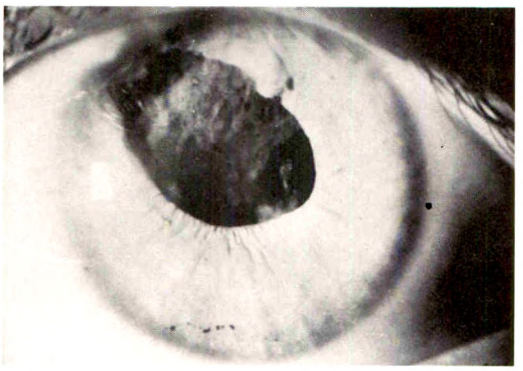

Fig. 9 (Kaufman). Aphakic eye in a 14-year-old patient before epikeratomileusis.

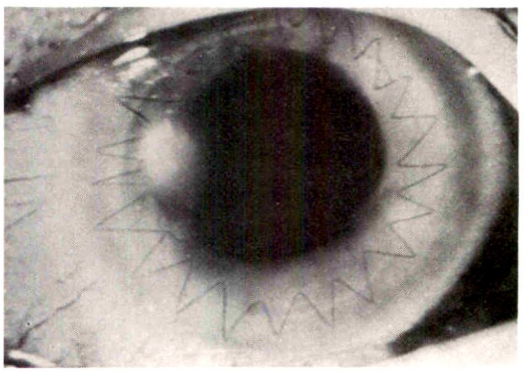

Fig. 10 (Kaufman). Same eye one day after receiving epikeratomileusis.

could be ordered and sutured to the recipient cornea with our relatively simple surgical procedure. The patient's own central cornea would be undamaged, and the living lens could be removed if necessary. Children as well as adults are suitable patients.

We are still in the early phase in our experience with patients (Figs. 9-12), but results are encouraging, and we hope that this modest extension of Barraquer's original concepts makes this a generally useful approach. As coroners' laws become more widespread, making more tissue available, and with the realization that older tissue, even if kept for several days and otherwise unusable for penetrating keratoplasty, can be perfectly adequate for these procedures, it seems likely that donor material for this procedure can be obtained, and a centralized source of preground corneal buttons can be made available.

I am enthusiastic about a procedure such as this, especially because it appears to be so simple and safe. However, this technique is new and experimental, and only time will tell whether my enthusiasm is appropriate.

SUMMARY

Major advances in the correction of aphakia have been made in the past few years. Extended-wear contact lenses constitute one advance, if not a perfect one. Intraocular lenses are now safer to use, and new research is seeking ways to improve their safety through protection of the corneal endothelium during surgery and stimulation of endothelial healing where damage does occur.

Altering the refractive power of the cornea offers another possible approach to the correction of aphakia. Modifications of Barraquer's keratomileusis procedure using preserved, preground corneas may have definite indications for certain types of aphakia, such as monocular aphakia in children and in individuals who would otherwise require secondary implants.

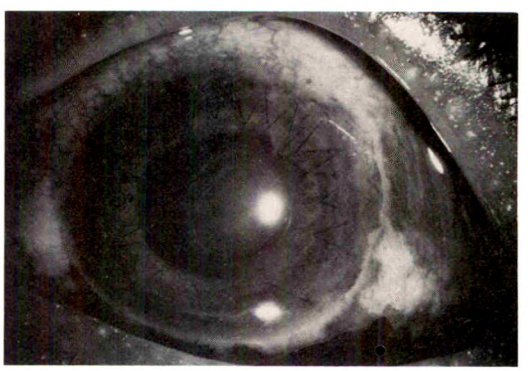

Fig. 11 (Kaufman). Eye of a 47-year-old patient two days after epikeratomileusis. Running suture is still in place.

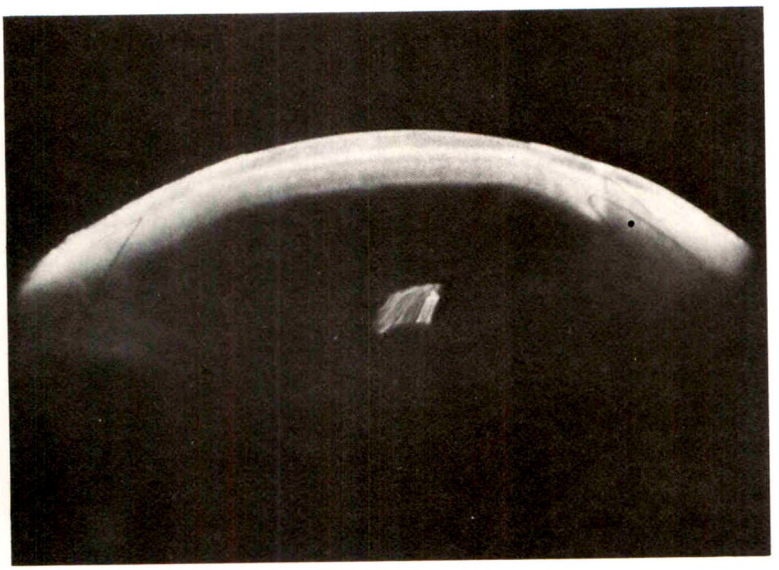

Fig. 12 (Kaufman). Slit-lamp photograph of same eye seen in Figure 11, showing donor tissue over Bowman's membrane.

We have experimented with a "living contact lens" of shaped donor tissue attached to the de-epithelialized surface of the eye. Such a lens of preground, preserved cornea tissue can be sutured to the patient's cornea with its central Bowman's membrane intact. A peripheral trephine mark is made, but the central cornea is untouched and the attachment of the living lens is simple. This procedure is apparently safe, and should be usable by any competent ophthalmic surgeon if the long-term results continue to be as encouraging as our early experience now suggests.

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SPECULAR MICROSCOPY OF IRIDOCORNEAL ENDOTHELIA SYNDROME

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The iridocorneal endothelial syndrome, which includes progressive essential iris atrophy, Chandler's syndrome, and the iris nevus (Cogan-Reese) syndrome, is characterized by abnormalities of the cornea, anterior chamber angle, and iris.[1] A defect of the corneal endothelium may be the fundamental change in this spectrum of disease, which leads to corneal edema in some cases and to the growth of a membrane onto the iris.[2,3] Contraction of the membrane may cause peripheral anterior synechiae with secondary glaucoma and the variable iris changes. The corneal endothelial defect has a fine beaten-silver appearance by slit-lamp biomicroscopy, and ultrastructural studies of cases with advanced corneal edema show scant, abnormal cells lining a thickened, multilayered Descemet's membrane.[4,5]

Histologic studies of the corneal endothelium in the iridocorneal endothelial syndrome have been confined to specimens from patients with advanced corneal edema. Using specular microscopy, we examined in vivo the corneal endothelium in 17 patients in whom the iridocorneal endothelial syndrome was at an early state of the corneal disease in which corneal clarity and pachometry were normal.

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital, Baltimore, Maryland (Drs. Hirst, Quigley, and Stark), and Duke University, Durham, North Carolina (Dr. Shields). This study was presented in part at the meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, April 30, 1979. This study was supported in part by Public Health Service Research Grants EY 02476 (Dr. Hirst) and EY 02120 (Dr. Quigley) from the National Eye Institute, National Institutes of Health.

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SUBJECTS AND METHODS

Patient group—A total of 17 patients were examined (Table 1), all of whom had previous diagnoses of either Chandler's syndrome, progressive essential iris atrophy, or iris nevus (Cogan-Reese) syndrome. Except for Cases 5, 7, 9, and 10, the patients in this study have been included as cases reported in a clinical study of the essential iris atrophies.[5,6] All 17 patients had unilateral ocular disease. Six patients had minor changes in the corneal endothelium on the unaffected side, determined by slit-lamp examination. None of the patients had a family history of ocular disease, nor any of the typical endothelial blister or vesicular changes of posterior polymorphous endothelial dystrophy.

Examination technique—All patients were examined by two of us (L.W.H. and H.A.Q.). The order of examination was specifically designed to allow maximum efficiency of each test. Visual acuity test, general slit-lamp examination, pachometry, and visual field measurements were followed by slit-lamp photography, clinical specular microscopy examination of both eyes, applanation tonometry, gonioscopic examination, and dilated-pupil examination of the fundus.

An average of 35 photographs were taken of each cornea by one of us

TABLE 1

CLINICAL HISTORY AND EXAMINATION OF AFFECTED EYES

Patient No., Age (yrs), Race, Sex	Diagnosis	Years Since Diagnosis	Eye	Slit-lamp; Cornea	Specular Microscopy Grade (1-3)	Pachometry (mm)
1, 27, W, F	Chandler's syndrome	4	L	Many dots	3	—
2, 35, W, F	Progressive essential iris atrophy	3	R	Central dots	3	—
3, 34, W, F	Chandler's syndrome	3	L	Central dots	3	0.53
4, 41, W, F	Chandler's syndrome	5	R	Many dots	2	—
5, 31, W, F	Chandler's syndrome	4	L	Many dots	2	—
6, 58, W, F	Iris nevus syndrome	6	L	Normal	Huge cells	—
7, 34, W, F	Chandler's syndrome	1/2	R	Few dots	3	—
8, 27, W, F	Progressive essential iris atrophy	8	R	Central dots	1-2	0.54
9, 35, W, F	Chandler's syndrome	4	R	Many dots	1	0.47
10, 44, W, F	Chandler's syndrome	20	R	Fine dots	2	—
11, 20, W, F	Progressive essential iris atrophy	9	L	Central dots	3	0.49
12, 53, W, F	Chandler's syndrome	4	R	Graft	Huge cells	0.56
13, 33, W, F	Progressive essential iris atrophy	9	R	Central dots	2	0.51
14, 50, W, F	Progressive essential iris atrophy	32	L	Graft	Huge cells	0.61
15, 50, W, F	Chandler's syndrome	4	R	Bullous	—	—
16, 55, W, F	Chandler's syndrome	26	L	Many dots	1-2	—
17, 60, W, F	Progressive essential iris atrophy	20	L	Many dots	3	0.53

(L.W.H.) using the Syber specular microscope and the method of Bourne and Kaufman.[7] Initially, we attempted to obtain both central and peripheral endothelial photographs. In the cases in which peripheral views could be taken, no added information was obtained and the quality of photography was poor. Fewer than 25% of the photographs were discarded because of poor photographic quality. The external centering of the applanation cone equidistant from the corneoscleral limbus for taking the photographs placed the endothelial areas viewed within the central 4 or 5 mm of the cornea. The clinical specular micrographs were reviewed by two of us (L.W.H. and H.A.Q.) and features common to the affected en-

Treatment	Visual Acuity	Increased I.O.P.	Field Loss	Approximate Angle Occlusion, %
None	6/5 (20/15)	No	No	25
None	6/6 (20/20)	Yes	No	50
Epinephrine 2%, sodium chloride drops	6/7.5 (20/25)	Yes	No	50
Epinephrine 2%, timolol 5%, acetazolamide	6/6 (20/20)	Yes	No	90
Pilocarpine, epinephrine	6/24 (20/80)	Yes	—	—
Glaucoma operation	6/7.5 (20/25)	Yes	Yes	95
Timolol	6/12 (20/40)	Yes	—	60
Pilocarpine 2%, epinephrine	6/6 (20/20)	Yes	Yes	100
Echothiophate iodide, timolol, methazolamide	6/12 (20/40)	Yes	Yes	25
Pilocarpine	6/6 (20/20)	No	No	50
None	6/6 (20/20)	No	No	25
Pilocarpine 1%, glaucoma-operation, penetrating keratoplasty	6/60 (20/200)	Yes	Yes	50
4 glaucoma operations	6/60 (20/200)	Yes	Yes	100
Pilocarpine, sodium chloride drops, acetazolamide, penetrating keratoplasty	1/60 (1/200)	Yes	Yes	100
Pilocarpine, epinephrine, corticosteroid drops, acetazolamide	6/60 (20/200)	Yes	Yes	75
Pilocarpine 4%, epinephrine 1%, sodium chloride drops, acetazolamide	6/7.5 (20/25)	Yes	Yes	75
Pilocarpine, sodium chloride drops	3/60 (3/200)	Yes	Yes	90

dothelia were noted and studied. Additionally, the specular micrographs of the unaffected corneas were subjectively assessed as to the regularity of the endothelial mosaic in relation to the age of the patients (Table 2). We devised a rough grading system, from 1 through 3, for the affected corneas (Table 3).

To assess the specificity of the endothelial changes in the affected corneas, specular micrographs of endothelia with typical changes of the iridocorneal endothelial syndrome were presented in a masked fashion to one of us (L.W.H.), together with specular micrographs of other endothelial conditions such as those of posterior polymorphous endothelial dystrophy, Fuchs' dystrophy, cornea gut-

TABLE 2

CLINICAL EXAMINATION OF CONTRALATERAL EYES

Patient No.	Eye	Slit-lamp; Cornea	Specular Microscopy; Cornea	Pachometry	Comments
1	R	Faint dots	Normal	—	—
2	L	Normal	Mild pleomorphism	—	—
3	R	Normal	Mild pleomorphism	0.55	—
4	L	Normal	Mild pleomorphism	—	—
5	R	Some dots	Normal	—	—
6	R	Normal	Mild pleomorphism	0.49	Increased IOP; epinephrine, 1%
7	L	Normal	Gross pleomorphism	—	Increased IOP;
8	L	Normal	Mild pleomorphism	0.52	—
9	L	Few dots	Mild pleomorphism	0.50	—
10	L	Normal	Normal	—	—
11	R	Normal	Mild pleomorphism	0.46	—
12	L	Normal	Gross pleomorphism	0.52	—
13	L	Normal	Normal	0.46	—
14	R	Normal	Normal	0.52	—
15	L	Few dots	Mild pleomorphism	—	—
16	R	Some dots	Mild pleomorphism	—	—
17	R	Some dots	Pleomorphism and cornea guttata	0.51	—

tata, direct corneal endothelial trauma, penetrating keratoplasty, keratic precipitates, Rieger's syndrome, and normal corneal endothelium.

RESULTS

All of the 17 patients included in this study shared the common features of the aforementioned triad of corneal abnormalities, broad peripheral anterior synechiae often extending to or beyond Schwalbe's line, and iris abnormalities. Additionally, those cases designated as progressive essential iris atrophy showed prominent hole formation in the iris. The one case of iris nevus (Cogan-Reese) syndrome was noteworthy for the clusters of pigmented nodules on the iris. Three patients with Chandler's syndrome also had areas of typical nevus formation.

TABLE 3

GRADING OF SPECULAR MICROSCOPIC ENDOTHELIAL CHANGES

Grade	Endothelial Changes (Uniform Throughout Central Cornea)
1	Rounding of endothelial cell angles Loss of hexagonal cell shape Early intracellular black-out areas
2	Increasing cellular pleomorphism Increasing intracellular black-out areas
3	Loss of cellular mosaic Black-out areas predominate
3	Loss of cellular mosaic Black-out areas predominate Mirror-imaging cellular outlines

Nine of the 17 patients had significant glaucomatous visual field loss. There was no distinct correlation between the degree of angle involvement by peripheral anterior synechiae and the occurrence of glaucomatous field changes. Remarkably good vision was maintained in all but five of the affected eyes despite extensive corneal endothelial changes in all the eyes.

Although six of the patients were thought to have minor endothelial changes by slit-lamp examination in the unaffected eye, all of the 17 patients were mainly unilaterally affected. Careful slit-

lamp examination of the endothelium revealed the beaten-metal appearance. This was difficult to differentiate from confluent cornea guttata, although (with the exception of Cases 14 and 15) the corneal clarity and thickness were entirely within normal limits in our patient group.

Fourteen of the 17 patients showed a similar spectrum of endothelial changes by clinical specular microscopy of the affected cornea. All the endothelial cells visualized on each of the photographs appeared to be uniformly affected by the disease process in that particular cornea. There were no areas of normal endothelial mosaic separating areas of affected endothelial cells.

In Grade 1 (minimally affected corneas) the early changes noted were a rounding-up of the endothelial cells, with not as sharp a definition of the hexagonal shapes, loss of the hexagonal shape with more pentagonal cells becoming evident, greater granularity of the intracellular details, and the appearance of small eccentric dark areas in the individual cells (Fig. 1). These changes affected virtually all of the cells studied in all of the photographs. Peripheral photography (within 3 to 4 mm of the corneoscleral limbus) confirmed that these cells also had the same morphologic changes as those seen centrally. Cases in Grade 2 (moderately affected corneas) had increased pleomorphism of the endothelial cells, with numerous kite-shaped cells (often oriented around a small cell), and enlargement of the dark areas or black-out areas within cells. These blacked-out areas would sometimes extend to the cell margin but

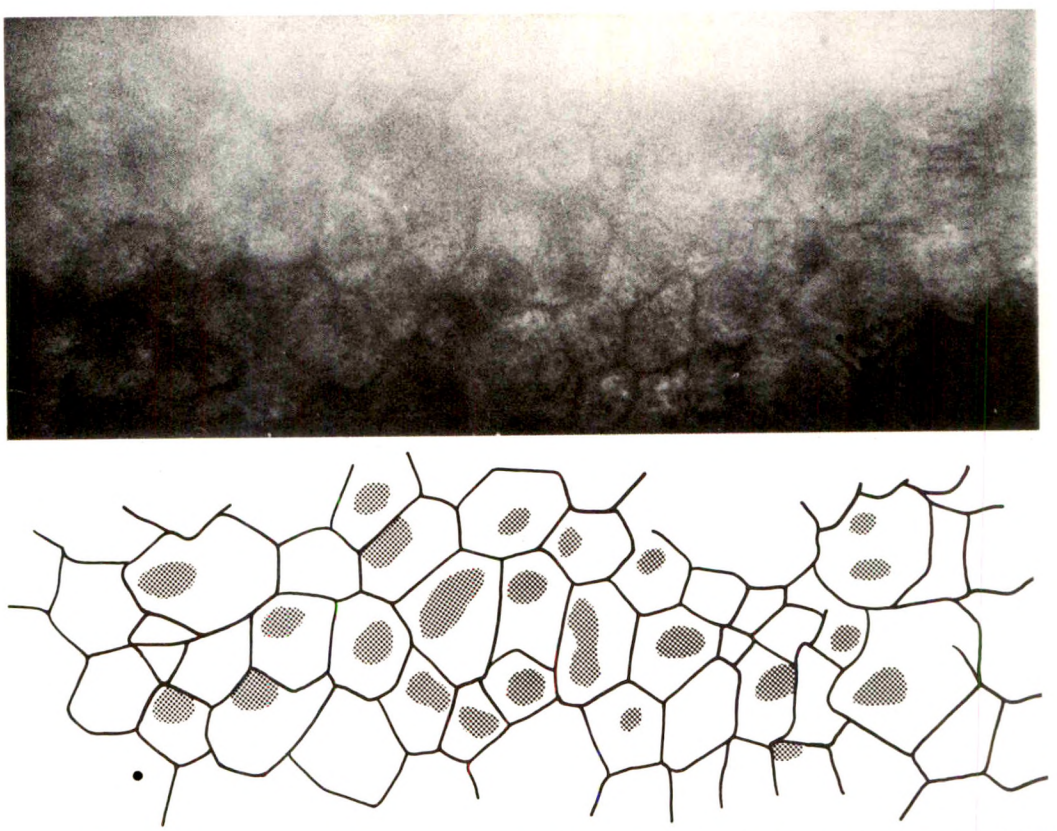

Fig. 1 (Hirst and associates). Case 9. Right eye. Specular microscopy and schema of Grade 1 endothelial changes.

did not appear to cross cell boundaries (Fig. 2). In Grade 3 (markedly affected corneas), the endothelial layer was no longer recognizable as a mosaic of cells, although careful examination indicated that the blacked-out areas within cells were abutting each other rather than crossing cell boundaries, and there was mirror imaging of the cell pattern (Fig. 3). Even with this degree of endothelial morphologic abnormality, a clear endothelial visualization could be obtained and good photographs taken.

In all of these stages of endothelial abnormality, a great degree of uniformity existed throughout each of the 35 or more photographs taken from any one cornea. We also found marked similarity between different corneas that were judged to have the same grade of abnormality. No significant difference in the endothelial morphology and abnormalities in patients with Chandler's syndrome as compared with essential iris atrophy patients was noted. However, in the one patient with iris nevus syndrome, the endothelial cells were abnormally large, with considerable pleomorphism, but without the other features described above. This appeared to be a uniform change throughout the areas photographed, with no areas of gross endothelial distortion.

The two patients who had had penetrating keratoplasty in the affected eye showed changes similar to those seen in other keratoplasty patients: enlarged, slightly pleomorphic cells, but with no evidence of recurrence of the iridocorneal endothelial abnormalities.

Of the six patients who were thought clinically to have some minor endothelial changes in the cornea of the unaffected

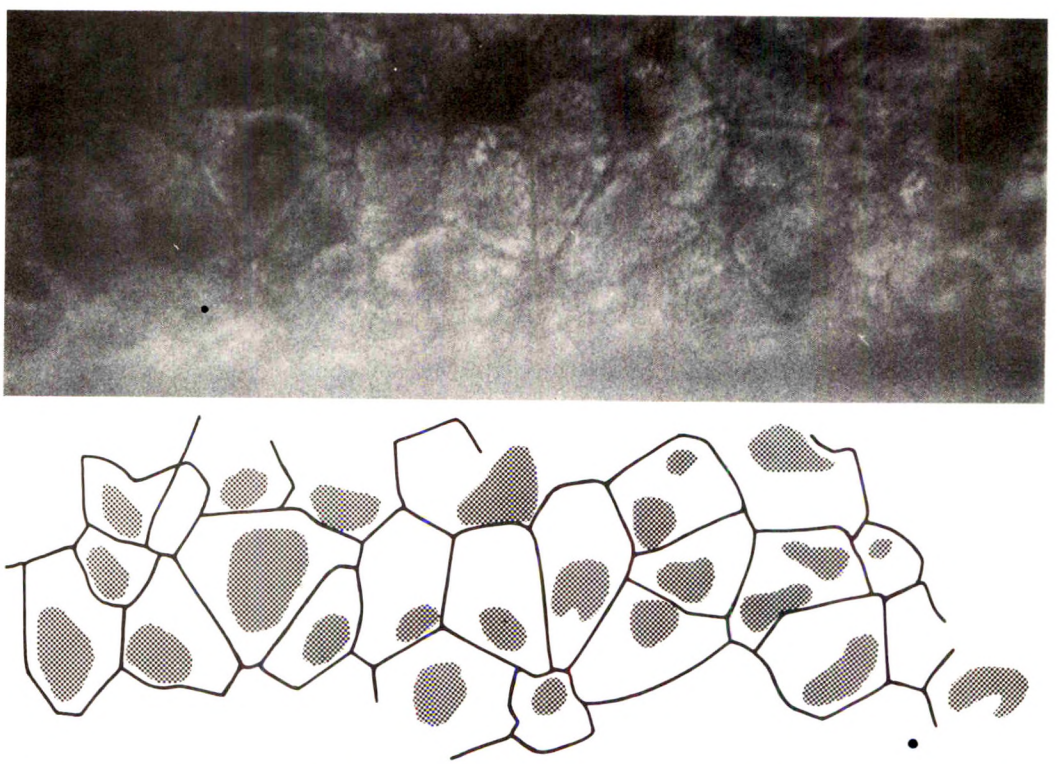

Fig. 2 (Hirst and associates). Case 10. Right eye. Specular microscopy and schema of Grade 2 endothelial changes.

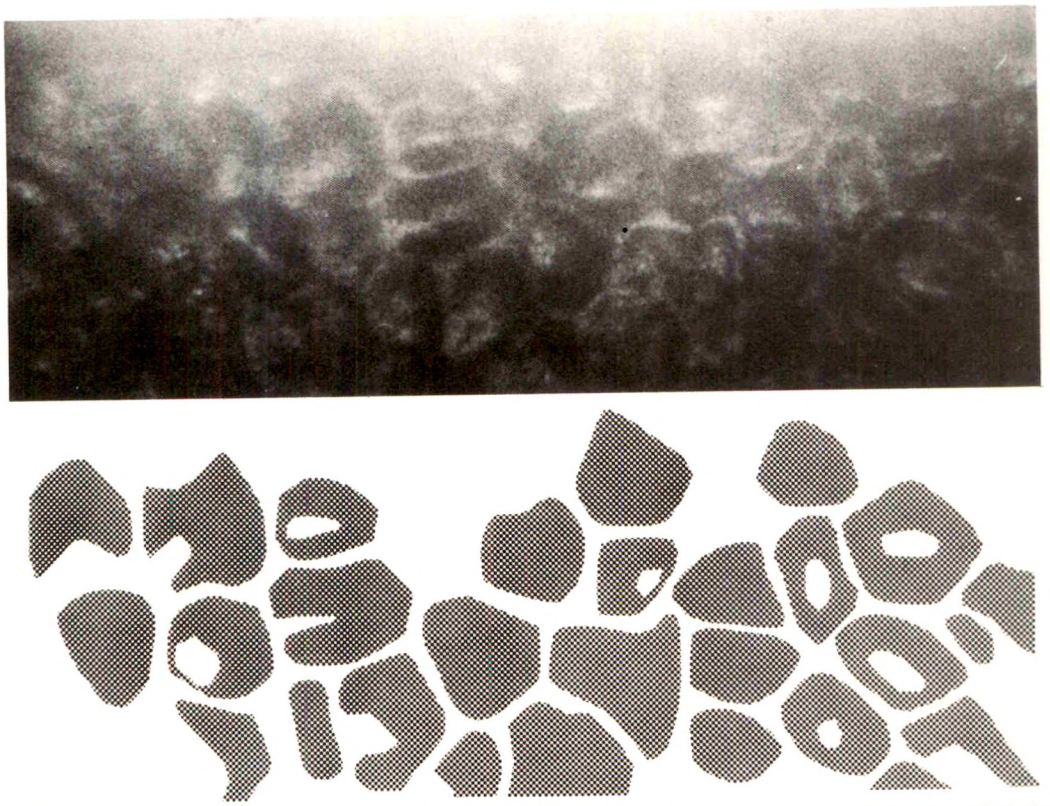

Fig. 3 (Hirst and associates). Case 11. Left eye. Specular microscopy and schema of Grade 3 endothelial changes.

eye, three showed distinct endothelial pleomorphism by specular microscopy, one had typical cornea guttata, and two appeared to be entirely normal. However, of the other 11 patients who were thought to have normal endothelia by slit-lamp examination of the unaffected eye, eight showed considerable endothelial cell pleomorphism by specular microscopy (Fig. 4), whereas only three were essentially normal.

Despite widespread and gross endothelial distortion, most of the affected corneas maintained a normal corneal thickness and clarity, although one patient had bullous keratopathy that prevented visualization of the endothelium by specular microscopy.

We found no relation between the known duration of the disease and the degree of endothelial abnormality, and also no apparent relation between the degree of pleomorphism in the unaffected eye and the duration of the disease in the affected eye. Even in patients with minimal to moderate angle involvement, specular microscopy of the central endothelium sometimes revealed Grade 3 endothelial changes.

In the masked recognition of endothelial photographs from patients with the iridocorneal endothelial syndrome, the observer (L.W.H.) was able to differentiate the iridocorneal endothelial photographs correctly from those of the other abnormal endothelial states in 15 of 17 eyes. In the two misidentified cases, the extreme degree of involvement by the

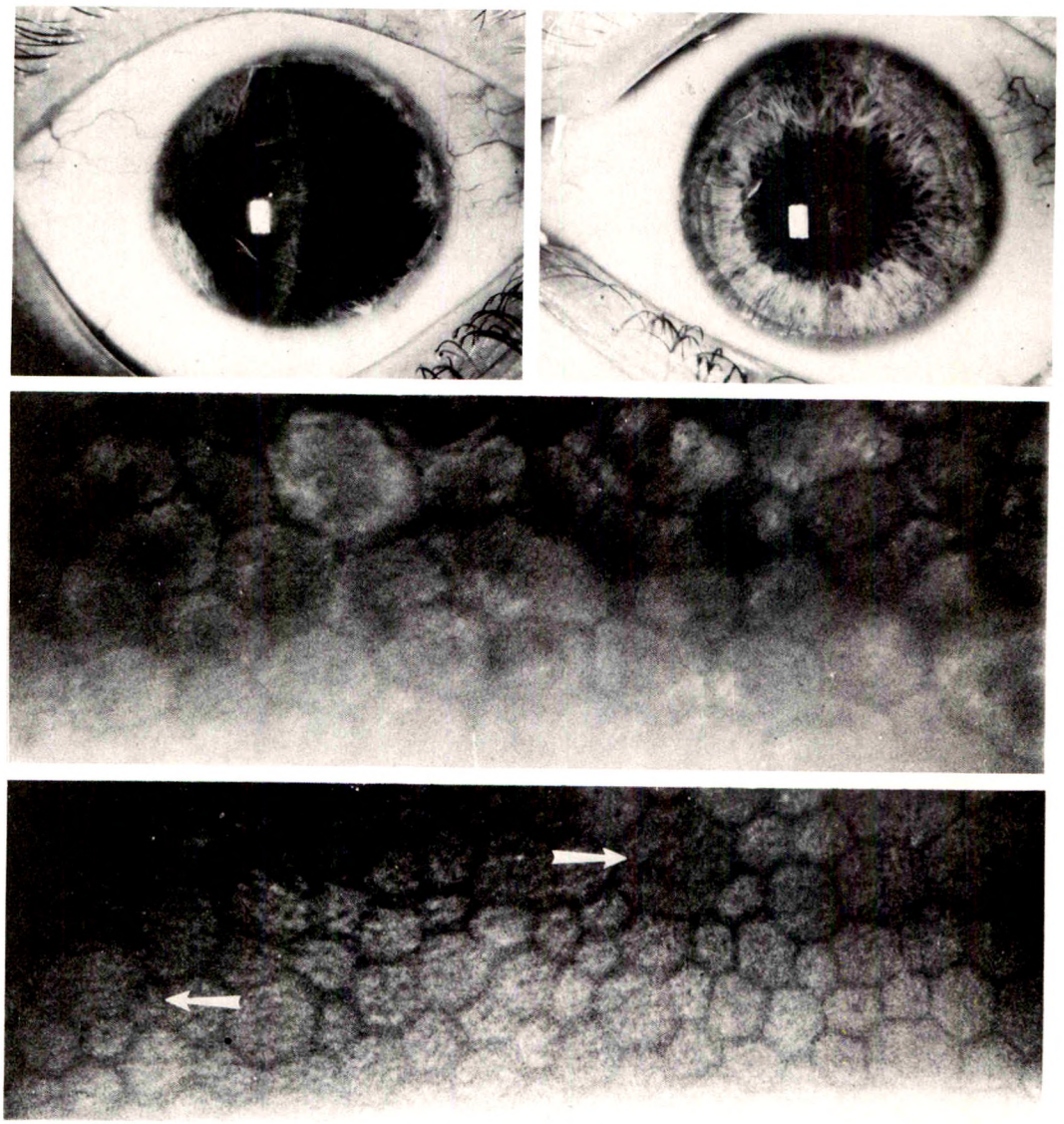

Fig. 4 (Hirst and associates). Clinical photographs and corresponding specular micrographs of the affected right eye (top left and center) and unaffected left eye (top right and bottom) in Case 8. Arrows indicate the largest and smallest cell size in specular micrograph from clinically unaffected eye of this 27-year-old patient (bottom).

iridocorneal endothelial syndrome left few typical features to differentiate it from severe Fuchs' dystrophy.

Discussion

The clinical assessment of the 17 patients included in this study confirms previous findings of the common features in these three syndromes.[1,3,5,6] The slit-lamp appearance of the endothelium does not appear to be diagnostic in these conditions, and the changes can be readily confused with cornea guttata, except for the unilateral tendency in the present group. The maintenance of excellent vision in most of these patients, even in the

face of severe endothelial abnormalities, suggests an entirely different anatomic and functional change in these endothelia as compared to the diffuse involvement in Fuchs' dystrophy. Although a previous report[8] suggested that the specular microscopic changes in Chandler's syndrome can be confused with cornea guttata, we found that the clinical specular microscopic appearance in the iridocorneal endothelial syndrome is distinguishable from other diseases involving the endothelium that are observable by specular microscopy, except for extreme degrees of the iridocorneal endothelial syndrome and Fuchs' dystrophy.

Only one patient in the 17 studied had bullous keratopathy that made endothelial visualization impossible. All the other corneas maintained normal thickness and clarity, and the endothelial layer was easily observed. This is unlike the observation of confluent cornea guttata in Fuchs' dystrophy, in which minimal corneal edema will often obscure underlying endothelial abnormalities. Although early corneal edema with slight intraocular pressure rise has been reported as one of the features of Chandler's syndrome,[5,9] this edema was previously noted early in the morning, whereas our patients were examined later in the day.

In many of our patients, most of the anterior chamber angle on gonioscopic examination was closed by peripheral anterior synechiae, and the endothelial abnormalities were advanced. In two affected eyes (Cases 1 and 9), less than 25% of the angle was involved, yet the central endothelial abnormalities were of similar severity to those of eyes with greater angle closure. Although more patients with early involvement should be examined, considerable endothelial abnormality in the central cornea can occur before extensive formation of peripheral anterior synechiae. Thus, the endothelial changes may be primary in this condition, with peripheral anterior synechiae, iris atrophy, and iris nodule or nevus formation occurring secondary to endothelial migration onto the anterior iris surface.

In our patient with the iris nevus syndrome, the appearance of the endothelium by specular microscopy was different from that of all the other patients. This patient also had a late age of onset, bilateral glaucoma (with an open angle in the eye unaffected by iris nevus syndrome), and has had filtration surgery on the affected eye. Therefore, this patient's eye may not be representative of all eyes with the iris nevus syndrome. Further specular microscopic studies are needed to determine whether there is a different, or similar, endothelial abnormality in the iris nevus syndrome as compared to the other two iridocorneal endothelial syndrome entities.

Although the iridocorneal endothelial syndrome may represent another of the mesodermal dysgenesis states, the ready diagnosis by specular microscopy of the two patients with Rieger's syndrome who were at first erroneously included in our study group suggests that the endothelial abnormalities differ in these two groups.

Although our finding of endothelial cell pleomorphism in the unaffected eyes cannot yet be substantiated quantitatively, our definite qualitative impression that the degree of pleomorphism was out of proportion to the age of the patient raises the possibility that there is bilateral (although unequal) involvement of the eyes in many, if not all, patients with the iridocorneal endothelial syndrome. Bilateral involvement has previously been clinically observed in essential iris atrophy and Chandler's syndrome.[4,6,10,12] We have no explanation from our clinical findings in this study for the usual increased involvement unilaterally. We do not believe that the increased endothelial changes can be accounted for by topical medication or surgery. Although the pa-

tients in Cases 1, 2, and 11 had not received ocular medications or surgery, they demonstrated typical endothelial changes, whereas in Case 6, the use of epinephrine produced no evidence of changes similar to the iridocorneal endothelial syndrome. Only a long-term study can enable us to determine whether the endothelial changes in either the initially affected or in the clinically uninvolved eye increase in severity with the duration of the disease.

There are numerous methodologic problems with clinical specular microscopy as a quantitative and qualitative method for endothelial studies. In particular, sampling difficulties and observer bias make attempted quantitation of unproved value in endothelial states in which the regular mosaic pattern has been lost. In the present study, the consistent widespread nature of the endothelial changes in all areas viewed—often, two to three times the number of areas viewed than were photographed—suggests, however, that valid qualitative statements can be made about the structure of the endothelium in the iridocorneal endothelial syndrome. The failure to observe gross endothelial changes in the unaffected eyes by clinical specular microscopy, despite apparent slit-lamp abnormalities, could well be related to the sampling problems with the clinical specular microscope.

The failure of the clinical specular microscope to show adequately the peripheral endothelium in affected eyes limits the observation of endothelial changes close to the areas where the broad peripheral anterior synechial adhesions occur. Despite published reservations about this method for quantitative examination of the endothelium in various pleomorphic endothelial states, the qualitative use of this machine in disease states in which the endothelium appears to be diffusely involved is valid. In this study we were able to use the specular microscope to differentiate mesodermal dysgenesis (Rieger's syndrome), Fuchs' dystrophy, and traumatic endothelial changes from the changes of the iridocorneal endothelial syndrome.

Summary

Clinical specular microscopic examination of 17 patients with features common to the iridocorneal endothelial syndrome (including Chandler's syndrome, iris nevus syndrome, and essential iris atrophy) showed pathognomonic endothelial changes and no areas of normal endothelial mosaic. Even in those patients with minimal anterior synechiae, gross central endothelial changes could be found, suggesting that the endothelial changes are primary and not secondary to the iris-corneal adhesions. Specular microscopy of the clinically uninvolved contralateral eye in these patients revealed frequent endothelial cell pleomorphism incommensurate with the patient's age. This study also confirmed the value of the specular microscope for qualitative endothelial observations.

Acknowledgments

John Payne, M.D., referred Case 5; W. Jackson Iliff, M.D., referred Case 7; Irvin Pollack, M.D., referred Case 9; and A. Edward Maumenee, M.D., referred Case 10.

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Fifty years ago this month in The Journal:

THE ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

After several meetings and much discussion of the possibilities, needs, and feasibility of such an organization, the Association for Research in Ophthalmology has completed its preliminary organization, and proposes to hold its first meeting for one day during the meeting of the American Medical Association in Detroit in June. The day of the meeting will probably be Tuesday the twenty-fourth. The Association is modeled on the similar Association for Research in Neurology. It is proposed to have one meeting a year, for one or two days, and to devote the time to the consideration of one subject, which will be covered from different angles by different contributors.

Am. J. Ophthalmol. 13:52, 1930

MANAGEMENT OF THYGESON'S SUPERFICIAL PUNCTATE KERATITIS

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Thygeson's superficial punctate keratitis is a well-defined clinical entity.[1–6] It occurs at any age and manifests as bilateral, coarse punctate opacities that stain variably with fluorescein. The course is characterized by multiple exacerbations and remissions, which continue for at least three years before all signs and irritative symptoms disappear.[1–4] The disease has been shown to continue in one patient for 16 years without healing. In this patient, subepithelial scarring was observed, possibly because of the prolonged presence of the epithelial lesions.[7]

The only known treatment for Thygeson's superficial punctate keratitis is topically applied corticosteroids, which usually result in relief of the irritative symptoms and often resolves the epithelial lesions. Complications associated with the prolonged use of corticosteroids in this disease have been ocular hypertension and cataracts.[4] In view of the occasional ineffectiveness of corticosteroids,[5] their potential for complications, and the possibility of corneal scarring with the prolonged presence of the signs of this disease,[4,7] we present an alternative method for the treatment of Thygeson's superficial punctate keratitis.

CASE REPORTS

Case 1—A 31-year-old woman developed a foreign body sensation and epiphora in both eyes in January 1978. On examination she had characteristic findings of Thygeson's superficial punctate keratitis and was treated with topical corticosteroids. This resulted in partial resolution of symptoms for two weeks, however, her symptoms subsequently returned. Despite numerous therapeutic trials with various topical corticosteroids and antibiotics, she became increasingly symptomatic and complained of diminishing vision when referred to us in January 1979. On examination the best corrected visual acuity was R. E.: 6/21 (20/70) and L. E.: 6/60 (20/200). The only abnormalities noted with slit-lamp examination were numerous slightly elevated coarse punctate epithelial lesions that stained variably with fluorescein, and were randomly distributed over both corneas. The results of the remainder of the examination were normal. A superficial biopsy specimen of one of the epithelial lesions was obtained from the right cornea and a pressure patch was placed over the right eye. On the following day, a decrease in number and size of the lesions was noticed in the right cornea. The lesions recurred after three days with no further interventions, and resolved again after a second trial with patching for 24 hours. In February 1979, the patient was fitted with extended-wear soft contact lenses in both eyes and the epithelial lesions resolved almost completely with some residual subepithelial opacities (Figs. 1 and 2). Visual acuity improved to 6/12 (20/40) in both eyes.

Case 2—A 41-year-old man was examined in May 1979 because of a 16-year history of Thygeson's superficial punctate keratitis that had been diagnosed by Phillips Thygeson, M.D. The patient, a physician, treated himself with varying amounts of topical medrysone each day, which improved his vision but only partially relieved his constant foreign body sensation and mild photophobia. However, even with frequent applications of topical corticosteroids, he has never had complete relief of signs or symptoms. On examination his visual acuity was 6/6- (20/20-) in both eyes. The slit-lamp examination revealed approximately eight to ten coarse, punctate epithelial opacities in both corneas. The results of the remainder of the examination were normal. In May 1979, the patient was fitted with extended-wear soft contact lenses in both eyes, with immediate and total resolution of his discomfort. Within 36 hours the epithelial lesions disappeared except for faint superficial scars in the area of three of the opacities in the right eye and four in the left eye. The lenses were removed for 24 hours and the epithelial lesions reappeared. Recently, the patient has removed the lens before sleep each night and the lesions have not reappeared.

Case 3—A 12-year-old girl developed photophobia and foreign body sensation in both eyes during

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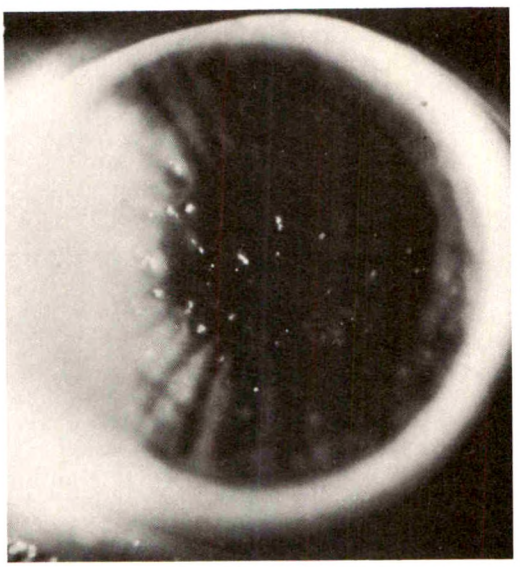

Fig. 1 (Goldberg, Schanzlin, and Brown). Case 1. Right cornea showing numerous coarse punctate epithelial opacities while being treated with daily topical corticosteroids.

August 1978. On examination she had many discrete, coarse epithelial lesions typical of Thygeson's superficial punctate keratitis in both corneas that responded to topical corticosteroids with disappearance of many of the lesions and relief of symptoms. In November 1978, the lesions returned and treatment with topical corticosteroids (Cortisporin) resulted only in symptomatic relief without clearing of the lesions. She was maintained on a regimen of topical corticosteroids (medrysone) four times a day until May 1979. At this time visual acuity was 6/9 (20/30) in both eyes with more than 15 epithelial opacities that stained variably in each cornea. Because of the persistence of the epithelial lesions, as well as the dependence on frequent topical corticosteroids to maintain symptomatic relief, the patient was fitted with extended-wear soft contact lenses (Bausch and Lomb Plano T), first in her right eye, and one week later, in her left eye. This has resulted in resolution of the epithelial lesions and symptomatic relief without medications up to the present time.

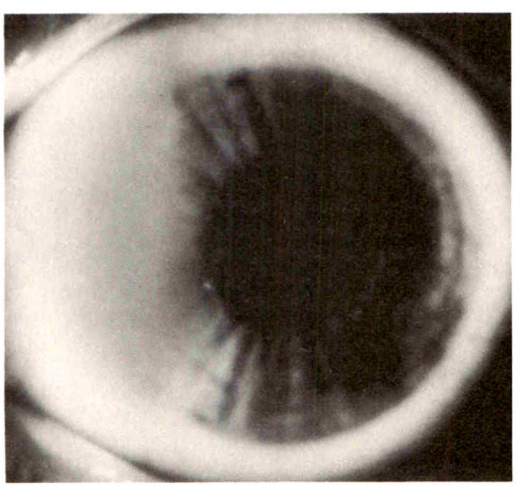

Fig. 2 (Goldberg, Schanzlin, and Brown). Case 1. Right cornea after 48 hours of soft-lens wear showing almost complete resolution of epithelial opacities.

Case 4—A 27-year-old man had an 11-year history of Thygeson's superficial punctate keratitis, which was originally diagnosed by Phillips Thygeson, M.D. He was treated with daily topical medrysone or fluorometholone regularly for many years. One year ago he stopped the use of topical corticosteroids because he was warned of the possible complications from their long-term use. Since then he has had recurrent episodes of irritation and blurring of vision averaging several days each month. In April 1979, he was first examined by us; he had best corrected visual acuity of R. E.: 6/9 (20/30) and L. E.: 6/12 (20/40). The slit-lamp findings were characteristic of Thygeson's superficial punctate keratitis, with multiple lesions randomly distributed over both corneas that showed variable staining with fluorescein. Two peripheral lesions had obvious associated scarring and one was vascularized. A pressure patch was applied over the left eye for 24 hours, and a marked improvement in symptoms and epithelial lesions was observed. Subsequently, the patient was fitted with several extended-wear soft contact lenses. Although the epithelial lesions resolved while wearing the lenses, the conjunctival vessels became hyperemic and the patient complained of discomfort after prolonged wear of the lenses. He has been scheduled for refitting of soft contact lenses for daytime wear.

DISCUSSION

In all four of our cases, rapid resolution of the epithelial lesions occurred with symptomatic relief after patching for 24 hours. Similarly, in all cases the use of therapeutic soft contact lenses resulted in almost complete resolution of the lesions, and dramatic immediate relief of discomfort. As yet, one of the patients (Case 4) has not been able to comfortably wear soft lenses for extended periods. The remaining three patients have tolerated extended wear of soft contact lenses accompanied by relief of both signs and symptoms. Removal of the lenses for 48

hours has resulted in return of the lesions. The follow-up period of these patients is too short to know if this approach to therapy will hasten the final resolution of the disease.

Although the mechanism of this response to patching or therapeutic soft contact lenses is speculative, the phenomenon suggests that exposure may be involved in the pathogenesis of the corneal epithelial lesions in Thygeson's superficial punctate keratitis. Previous studies have not conclusively shown an etiologic agent, although a viral cause has been suggested.[2, 8]

Prolonged presence of the disease appears to have the potential for subepithelial corneal scarring and vascularization,[7] and complications from the use of topical corticosteroids have occurred.[4] Additionally, corticosteroids do not always relieve the signs or symptoms of Thygeson's superficial punctate keratitis.[5] The use of therapeutic soft contact lenses may provide an alternative to topical corticosteroids in the treatment of Thygeson's superficial punctate keratitis. Forstot and Binder[9] reported the improvement and relief of symptoms in three patients. However, further study and longer follow-up is necessary before long-term use can be advocated.

Summary

Four patients had Thygeson's superficial punctate keratitis of one to 16 years' duration. One patient was completely unresponsive to topical corticosteroids, and the remaining three patients had only partial resolution of signs or symptoms while using topical corticosteroids. In all cases, rapid resolution of the epithelial lesions occurred with symptomatic relief after patching for 24 hours or after the use of therapeutic soft contact lenses. Three of the four patients have tolerated daily or extended wear of soft contact lenses accompanied by relief of both signs and symptoms.

The use of therapeutic soft contact lenses may provide an alternative to topical corticosteroids in the treatment of Thygeson's superficial punctate keratitis.

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ICHTHYOSIS HYSTRIX (EPIDERMAL NEVUS SYNDROME) AND COATS' DISEASE

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The epidermal nevus syndrome consists of any one or a combination of epidermal nevi described as nevus unius lateris, ichthyosis hystrix, linear nevus sebaceous, or congenital acanthosis nigricans. Additionally, adnexal tumors (organoid nevi) such as syringocystadenoma papilliferum (apocrine gland tumor), nevus sebaceous of Jadassohn, eccrine gland, and duct tumors are seen in these patients. Most cases arise sporadically but there is a suggestion of autosomal dominant transmission in some patients. Associated pigmentary disturbances, namely, hypopigmentation, café-au-lait spots, junctional nevi, and intradermal nevi, have been described as well as the vascular lesions of extranuchal nevus flammeus and cavernous hemangiomas. Fibrovascular lesions such as sclerosing hemangiomas and the cutaneous malignancies—keratoacanthoma, basal cell carcinoma, and squamous cell carcinoma—have also been reported.

Somatic anomalies largely involving the skeletal and central nervous systems have been noted with considerable frequency in the epidermal nevus syndrome. Primary anomalies of bone formation include incomplete formation of the ankle, foot, phalanges, and vertebrae; hypertrophy of the frontal bones, clavicles, and bones of the extremities secondary to localized giantism; or hypoplasia of the sphenoid bones, iliac wings, pubic bones, and long bones of the limbs. Secondary bony complications are atrophy, ankylosis, vitamin D-resistant rickets, and ameloblastoma in the mandible. Bone cysts have been described in the humerus, femur, tibia, and mandible. The effects of the bone changes are clinically manifest as limb hypertrophy, asymmetry of the skull and orbits, short limbs, talipes equinovarus, genu valgum, kyphoscoliosis, frontal bossing, saddle deformity of the nasal bridge, spontaneous fractures, rickets, brachydactylia, camptodactylia, and clinodactylia.

Central nervous system abnormalities include mental retardation, cortical atrophy, hydrocephalus, focal and grand mal epilepsy, hyperkinesia, cerebrovascular tumors (hemangioma, astrocytoma) and malformations, cerebrovascular accidents, hemiparesis, quadriplegia, cranial nerve and cranial nuclei abnormalities (mostly sixth, seventh, and eighth nerve involvement), and cortical blindness. Other abnormalities or diseases reported with the epidermal nevus syndrome are horseshoe-shaped kidney, decreased renal tubular reabsorption of phosphate, coarctation of the aorta, intrahepatic cystic biliary adenomas, patent ductus arteriosus, chronic upper respiratory tract infections, otitis media, and systemic malignancy at a young age including Wilms' tumor, nephroblastoma, bilateral salivary gland adenocarcinoma, carcinoma of the esophagus and stomach, and mammary adenocarcinoma.[1–4]

Ocular abnormalities have been noted as an important part of this syndrome. The ocular abnormalities tend to occur on the same side as the nevi but do not require the presence of nevi involving the face or scalp. Blepharoptosis and a fibroma on the bulbar conjunctiva have been described in a patient with a minimum

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paresis of the ipsilateral arm.[4] Blepharoptosis has been seen in a patient with oculomotor nerve palsy with pupillary sparing.[5] Antimongoloid eyelid fissures and eyelid colobomata have been reported as well as horizontal and rotary nystagmus, esotropia, and facial nerve paralysis.[6–8] Numerous descriptions of associated conjunctival tumors include epibulbar lipodermoids, bulbar dermoids with pannus formation, fibromata, teratoid tumors, choristomas, and hamartomas.[4,6,7,9,10] These tumors often contain aberrant lacrimal glands, sebaceous glands, cartilage, and immature hair follicles. Corneal opacities, corectopia and colobomata of the iris are also seen.[1,7]

These reports do not always include dilated ocular fundus examination. Ocular fundus findings described include chorioretinal colobomata, a markedly cupped optic disk without glaucoma, and peripapillary ectasia.[1,6,7,10] The case of a 10-year-old boy with extensive oral malformation described as "totally blind in the left eye and partially blind in the right eye," without further information concerning ocular examination, has been reported.[11] Another patient had bilateral lipodermoids of the conjunctivae, vascularization of the left cornea, bilateral superior colobomas of the irides, generalized retinal degeneration, and coloboma of the choroid and retina inferotemporal to the disk in the right eye, with no fundus details other than a red reflex visible in the left eye.[12]

We describe herein a 4-year-old girl with the ichthyosis hystrix variant of the epidermal nevus syndrome and ocular fundus findings of Coats' disease causing bilateral decreased visual acuity.

CASE REPORT

The patient was first seen here when she was 4 months old. The infant was full term and had had an uncomplicated delivery with a birth weight of 3,600 g (7 lb 15 oz). The mother had a history of epilepsy but was not taking anticonvulsant medication during the pregnancy. There was no history of maternal prenatal illness. The mother had noted an erythematous rash with blisters on the infant's face, neck, chest, back, arms, and legs at birth. Some of these lesions became hypopigmented after two to four months, whereas others on the face and neck became rougher to the touch and hyperpigmented. When first examined the infant had a weight, length, and head size that were within normal limits for her age. The occiput was somewhat flattened and development was thought to be delayed. Whorls of palpable, rough-textured, hypopigmented lesions were noted on the skin of the chest, back, and extremities with multiple verrucous hyperpigmented lesions on the face and neck. A submucous cleft in the posterior region of the hard palate and a bifid uvula were noted.

When she was 21 months of age, developmental evaluation showed a slight delay in all areas but visual discrimination in the 16-month-old age range was described as one of her strengths.

At the age of 25 months, an esotropia of the right eye, which measured approximately 20 diopters Hirschberg, was noted. When the left eye was occluded, nystagmoid movements were noted in the right eye and the patient had great difficulty in fixating with the right eye.

Further developmental evaluation at 35 months of age revealed good eye-hand coordination with an overall motor and mental level of age 15 months. When the patient was 4 years old, an otolaryngologic consultation was obtained because of recurrent upper respiratory tract infections and serous otitis media which seemed to impair the child's hearing. Antibiotic therapy was unsuccessful and bilateral myringotomies with the insertion of tubes were performed which dramatically improved the patient's hearing. The patient's blood pressure at this time was 104/60 mm Hg. Ophthalmological evaluation was also obtained but visual acuity measurement was not possible. Examination with the patient under general anesthesia with atropine retinoscopy revealed a refractive error in the right eye of plano $+3.00 \times 90$ and in the left eye $+2.00 +1.75 \times 90$. Corneal diameters were 10 mm horizontal and 9.5 mm vertical in each eye. The anterior segments were within normal limits and the intraocular pressure was 5/5.5 mm Hg (Schiøtz) in both eyes. Fundus examination with the pupils dilated using the indirect ophthalmoscope showed the presence of multiple hard yellow exudates with pigment mottling in the posterior pole and midperiphery of the right eye. There was a small focus of fibrous tissue near the foveola (Fig. 1). In the far periphery there were multiple saccular retinal vascular dilatations, telangiectases, and adjacent areas of small vessel nonperfusion with retinal edema, hard yellow exudates, and subretinal fluid creating a shallow peripheral retinal separation (Fig. 2). Some of the small peripheral retinal venules were sheathed. In the left eye there was a more extensive foveolar and macular hard yellow deposit with an overlying secondary retinal hemorrhage (Fig. 3). We noted diffuse hard yellow exudates in the posterior pole extend-

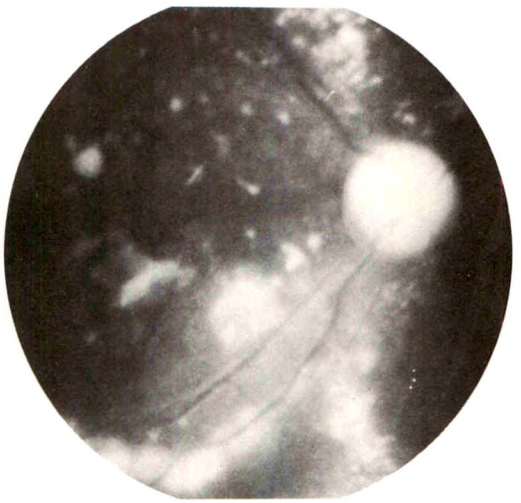

Fig. 1 (Burch, Leveille, and Morse). Fundus photograph of the right eye showing multiple hard yellow exudates in the posterior pole which were secondary to peripheral retinal vascular abnormalities.

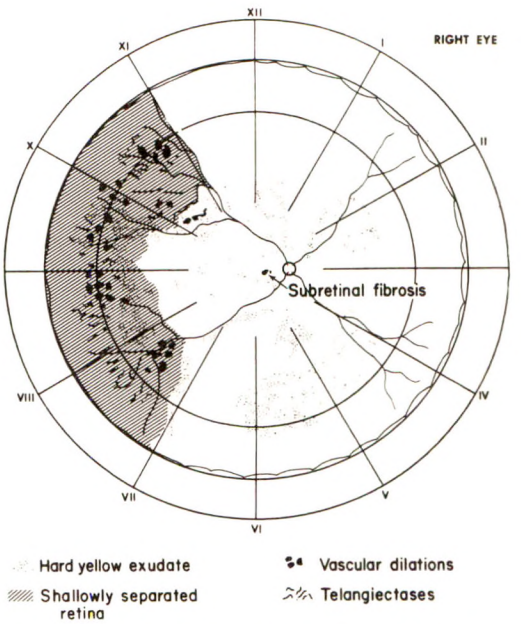

Fig. 2 (Burch, Leveille, and Morse). Fundus drawing of the right eye, showing saccular vascular dilatations and telangiectases (solid black), hard yellow exudate (dots), and peripheral shallow retinal detachment (lines).

ing slightly peripheral to the retinal vascular arcades with similar vascular telangiectases, small venule sheathing, saccular aneurysms, and areas of small vessel nonperfusion in the far periphery (Fig. 4). The findings in the left eye were less extensive.

Dermatology consultation confirmed the clinical diagnosis of ichthyosis hystrix with the previously described skin lesions (Figs. 5-7). Results of biopsies of multiple areas of the skin were consistent with a nonepidermolytic variety of systematized verrucous epidermal nevus.

Results of laboratory examination of the urine,

Fig. 3 (Burch, Leveille, and Morse). Fundus photograph of the patient's left eye showing much more extensive hard yellow exudate in the posterior pole with a secondary retinal hemorrhage just superior to the foveola.

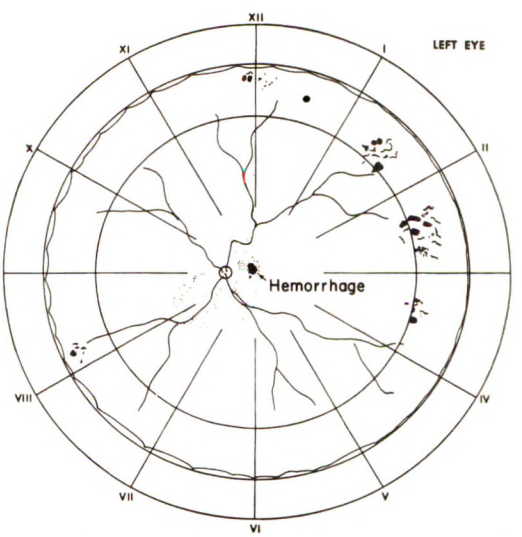

Fig. 4 (Burch, Leveille, and Morse). Fundus drawing of the left eye, with peripheral saccular vascular dilatations and telangiectases (black areas) and hard yellow exudate (dots).

Fig. 5 (Burch, Leveille, and Morse). Full-face photograph of the patient showing curvilinear verrucous hyperpigmented skin lesions most prominent on the nose and above the right eye. She had dressings on the ears after ear surgery.

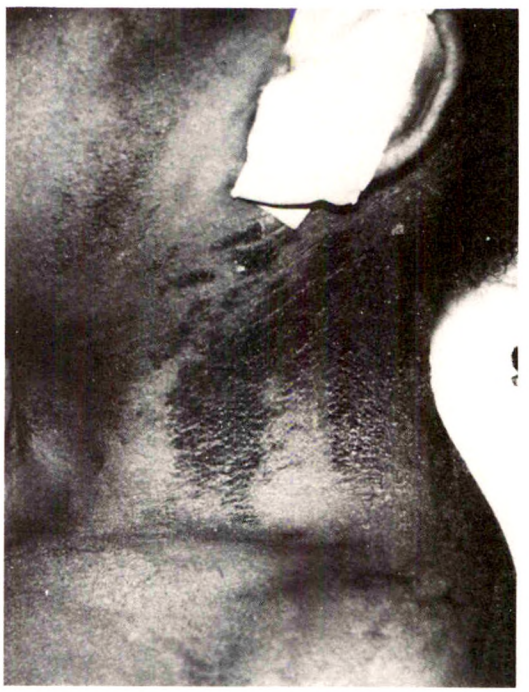

Fig. 6 (Burch, Leveille, and Morse). Photograph of the patient's neck showing additional hyperpigmented papillomatous skin lesions.

complete blood cell count, liver functions, and serum viscosity were within normal limits. Chest x-ray, computed axial tomography scan, and skull x-ray showing a brachycephalic skull shape, electrocardiogram, and electroencephalogram were unremarkable. Total cholesterol level was 105 mg/dl and triglyceride level was 65%. Protein electrophoresis showed a slight decrease in total protein level to 6.30 g/100 ml (normal, 6.5 to 7.9 g/100 ml); albumin, 3.03 g/100 ml (normal, 3.2 to 5 g/100 ml), and a slight increase in the α_2 fraction to 1.03 g/100 ml (normal, 0.3 to 1 g/100 ml), with other values within normal limits. Serum lipoprotein electrophoresis showed slight increase of α to 33.0% (normal, 3 to 25%); prebeta, 31.4% (normal, 10 to 25%), and an increase in β to 24.5% (normal, 40 to 65%). Hemoglobin electrophoresis showed hemoglobin α_2, 2.9%, and hemoglobin α, 97.1%.

The patient received cryotherapy to the areas of retinal vascular malformation, which resulted in a slow reabsorption and disappearance of the retinal edema and hard yellow exudate.

Discussion

The variants of the dermatologic syndrome now called the epidermal nevus syndrome have been previously described under many different names. Skin biopsy findings in these patients depend to some extent upon the site from which the biopsy specimen is taken and modified or different histopathologic findings are possible in the same patient when multiple biopsy specimens are obtained from different locations at the same time. Most patients with dermatologic problems are not seen for careful examination by ophthalmologists unless there is some manifest ocular abnormality.

Some previously reported cases lack adequate ophthalmologic evaluation when describing blindness of unknown cause,[11] or refer to generalized retinal degeneration,[12] a term which is not adequately descriptive.

The retinal vascular abnormalities in our patient suggest a possible relation to those vascular abnormalities or malfor-

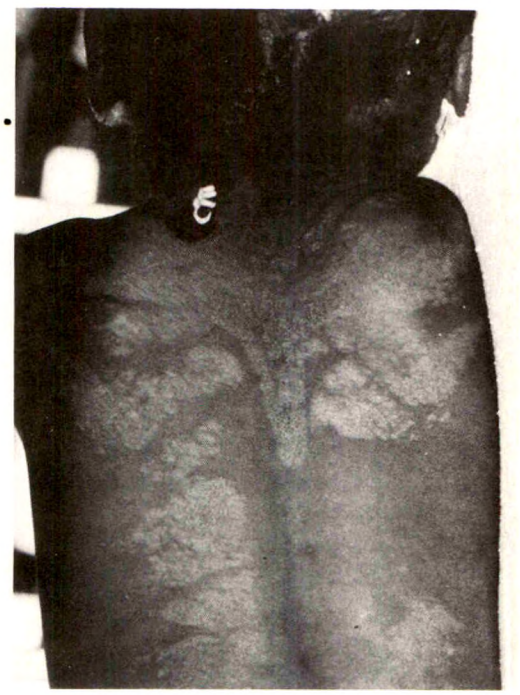

Fig. 7 (Burch, Leveille, and Morse). Photograph of the patient's back showing the configuration of the rough-textured hypopigmented skin lesions.

mations of the skin and central nervous system so commonly reported in this syndrome.

The retinal vascular changes described in Coats' disease (retinal telangiectasia, Leber's miliary aneurysms) are considered to be developmental anomalies with telangiectasia or saccular dilatation of the retinal vessels associated with areas of capillary and small vessel nonperfusion over a variable extent of the ocular fundus. The retinal vascular anomalies may decompensate at any age and the resultant increased vascular permeability may cause varying amounts of intraretinal edema, hard yellow exudate, and secondary transudative retinal separation which may impair central vision if the hard yellow exudate or retinal separation extend to involve the macula. The retinal vascular malformations described as Coats' disease are nonspecific. They may be related to other developmental abnormalities, as retinal vascular alterations or responses such as microaneurysms are not a finding isolated to one specific disease.

Our patient was severely handicapped because of decreased hearing and visual acuity, both of which might have been treated at an earlier age with prompt otolaryngologic and ophthalmologic consultation. A complete ophthalmologic examination including indirect ophthalmoscopy with scleral indentation should be part of the evaluation of all young patients with extensive cutaneous or other systemic malformations or anomalies. In patients with hard yellow exudates in the posterior pole a careful search of the fundus periphery for vascular abnormalities should be made. Occasionally, the hard yellow exudates are unrelated to nearby visible incompetent vascular malformations and are the result of lesions in the far retinal periphery. With adequate photocoagulation or cryotherapy of the peripheral vascular abnormalities the secondary retinal edema and hard yellow exudate will reabsorb over a period of weeks to months. Early treatment of incompetent, leaking peripheral retinal vascular malformations before secondary macular involvement may prevent loss of central vision.

Summary

A 4-year-old girl had the ichthyosis hystrix variant of the epidermal nevus syndrome with ocular fundus manifestations of Coats' disease. Her hearing was impaired because of serous otitis media and her visual acuity decreased because of hard yellow exudate in the macula as a result of decompensation and plasma leakage from the peripheral retinal vascular anomalies. Treatment of the vascular malformations with cryotherapy resulted in a reabsorption of the retinal edema and hard yellow exudate.

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BIRDSHOT RETINOCHOROIDOPATHY

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Many varieties of intraocular inflammation remain difficult to diagnose and treat. Maumenee[1] has emphasized the importance of the accurate delineation of syndromes, even though a causative agent is unknown and the pathogenesis may be uncertain at the time of description. Careful morphologic classification of previously undescribed entities provide a basis for further elaboration and comparison of such disorders by other observers. Examples of this approach are toxoplasmic retinitis, histoplasmic choroiditis, and nematode endophthalmitis. The classification of intraocular inflammation into entities is even of value in those instances where the pathogenesis and cause of the condition remain totally unknown. A typical example is the so-called pars planitis syndrome (peripheral posterior segment inflammation, vitreous opacities, and edema of the posterior pole),[2] which has variously been referred to as chronic cyclitis and peripheral uveitis, among other terms.[3–7] The value of accurately describing such entities of unknown pathogenesis and cause is that it allows the clinician to predict the course of the disease and to recognize deviations from the usual pattern. This approach should prevent the splitting of a single entity into multiple diagnoses based on secondary complications. The delineation of such clinical entities allows the clinical investigator to evaluate long-term follow-up, the usefulness of therapy, and even histologic correlations.[8–10]

The type of intraocular inflammation that we describe herein is characterized by many clinical signs common to pars planitis, but occurs in the absence of the characteristic vitreous changes overlying the pars plana and peripheral retina, particularly inferiorly. This new syndrome, birdshot retinochoroidopathy, has distinctive, multiple depigmented spots at the level of the retinal pigment epithelium. We present a morphologic description of this syndrome and case reports. It has been difficult to coin an appropriate, concise, yet encompassing term for this entity. The term birdshot retinochoroidopathy has been chosen because of the multiple, small, white spots that frequently have the pattern seen with birdshot in the scatter from a shotgun.

Birdshot retinochoroidopathy is characterized by a number of signs of intraocular inflammation common to pars planitis. These include: (1) a quiet eye, rarely red or injected, never painful; (2) minimal, if any, anterior segment inflammation, but occasional keratic precipitates on the corneal endothelium and angle, and occasional ray and cell; (3) chronic inflammation with cells or particulate matter in the vitreous, anterior as well as posterior; (4) retinal vascular leakage, particularly prominent in the perifoveal

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capillaries, which leads to cystoid macular edema and, occasionally, disk edema.

The clinical features that distinguish this syndrome from pars planitis include: (1) no snowballs or snowbank, that is, vitreous opacities overlying the pars plana, the classic sign of pars planitis; (2) cream-colored or depigmented spots, usually discrete and scattered throughout the fundus (Fig. 1). These depigmented spots, the most distinctive sign of this syndrome, appear at the level of the retinal pigment epithelium, but, on occasion, suggest an even deeper infiltrate. They do not have the atrophic appearance characteristically seen in the presumed ocular histoplasmosis syndrome. These spots can be confluent and actually appear to radiate out from the optic nerve in some instances.

Case reports

Case 1—A 35-year-old woman first came here in May 1955 with decreased vision and uveitis of at least three years' duration. At that time, her best corrected visual acuity was R.E.: 6/21 (20/70) and L.E.: 6/60 (20/200). The anterior segments showed no evidence of inflammation. She had bilateral cystoid maculopathy and a low-grade chorioretinitis. The optic nerve heads were normal. She returned in 1963, at which time visual acuity was less than 6/120 (20/400) in both eyes. Many cells in the anterior vitreous of both eyes were evident. Additionally, she had a serous detachment located approximately 7 disk diameters to the temporal side of the optic nerve head. No infiltrate over the pars plana was noted. The depigmented spots characteristic of this syndrome were scattered throughout the periphery of the fundus. In October 1975, her visual acuity had decreased to R.E.: 6/240 (5/200) and L.E.: 6/170 (7/200). Visual acuity had been stable at this level for four years, and the inflammatory reaction was as quiet as the referring physician had ever noted it to be. Posterior subcapsular cataracts had developed, but were not a significant factor in the patient's visual impairment. Vitreous cells and the characteristic depigmented spots persisted in both eyes. The optic nerves were pale and the vessels markedly attenuated. It was difficult to identify some of the major retinal arteries on ophthalmoscopic examination, although they were readily identified on fluorescein angiography. The visual fields were markedly constricted.

Case 2—In April 1964, a 36-year-old woman was referred here for examination after an eight-month history of decreased vision for which uveitis had been diagnosed. On examination at that time, visual acuity in the right eye was 6/4.5 (20/15) and best corrected visual acuity in the left eye was 6/7.5 (20/25). There were a few keratic precipitates and some particulate matter in the anterior vitreous of the left eye. Also noted were slight disk edema and dilatation of the retinal vessels, as is seen in the pars planitis syndrome, but there was no pars plana exudate inferiorly. Results of a systemic examination were unrevealing at that time.

Visual acuity dropped to R.E.: 6/7.5 (20/25) and L.E.: 6/12 (20/40) in June 1964. In August 1964, her visual acuity returned to R.E.: 6/6−2 (20/20−2) and L.E.: 6/9 (20/30). However, in September 1965, her visual acuity in the left eye had decreased to 6/60 (20/200). Fluorescein angiography showed dilated veins and diffuse capillary leakage in the macula. In November 1967, a large serous detachment of the sensory retina developed that covered 5 disk diameters in the left eye. In January 1972, visual acuity in the right eye had decreased to 6/12 (20/40). A course of 50 mg of prednisone per day and 400 rads of radiation to the posterior segment of both eyes was administered. Diffuse leakage from the retinal vessels, particularly the venular side of the retinal capillary network, persisted. As of January 1974, visual acuity was further decreased to R.E.: 6/24 (20/80) and L.E.: counting fingers at six inches. The classic depigmented spots of the birdshot retinochoroidopathy remained unchanged. A previous serous detachment of the right macula had settled spontaneously. In the left eye, there was a large serous detachment of the retina and disturbance of the pigment epithelium. The patient also developed a retinal hole superotemporally in the posterior pole of the left eye, which was successfully repaired with a scleral buckling procedure in April 1975. In April 1976, her visual acuity was R.E.: 6/60 (20/200) and L.E.: counting fingers. There were at no time any systemic or ocular signs to suggest Harada's syndrome.

Case 3—A 37-year-old woman had her first evaluation in August 1978 because of a four-year history of decreased vision and evaluation by a number of ophthalmologists in the previous three years for the signs of intraocular inflammatory disease. On ocular examination, visual acuity was R.E.: 6/6− (20/20−) and L.E.: 6/7.5+ (20/25+). The anterior segments were unremarkable. Ophthalmoscopic examination of the right eye showed numerous depigmented spots, particularly inferiorly. Vitreous debris was noted; however, no frank cystoid edema or optic nerve abnormality was noted. Ophthalmoscopic examination of the left eye revealed cystoid macular edema and possibly some engorgement of the optic nerve head. The characteristic depigmented spots were prominent. There was no pars plana exudate in either eye. The patient did not show any significant response to corticosteroid therapy.

Case 4—A 42-year-old woman was referred here because of decreased vision in her right eye. Her visual acuity had decreased from 6/6 (20/20) to 6/15 (20/50) in October 1966, two months before her initial examination here. On ocular examination, best corrected visual acuity was R.E.: 6/15 (20/50)

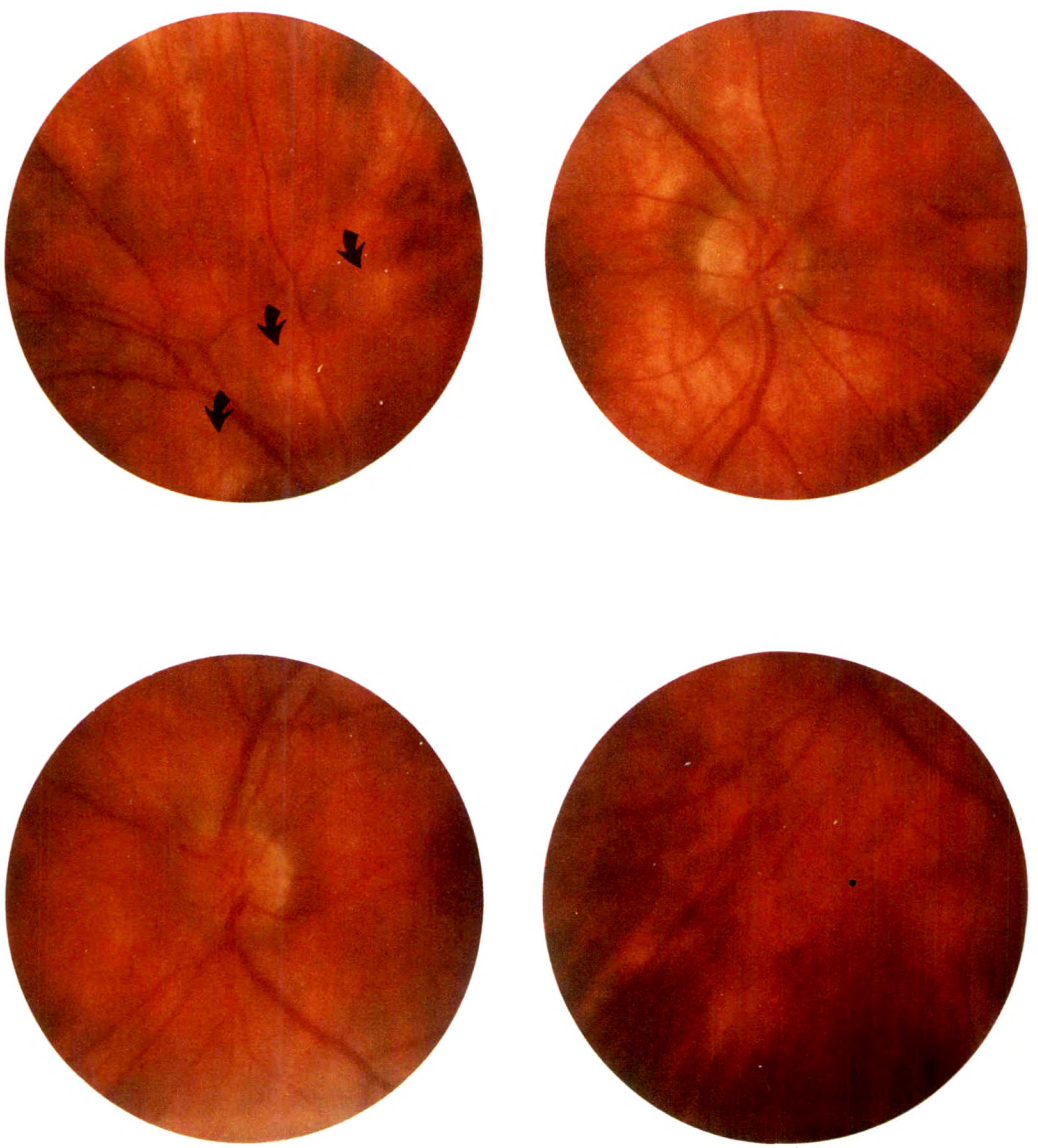

Fig. 1 (Ryan and Maumenee). Case 9. October 1977, two years after onset. Top left, Superotemporal to optic nerve in right eye. Apparent is the contrast in size in the discrete and confluent spots (arrows). Top right, Optic nerve in right eye. Note the discrete, cream-colored spots just nasal to the disk. Bottom left, Optic nerve in left eye. The intraocular inflammation has led to more opacity and a membrane, presumably inflammatory in origin, over the optic nerve. The discrete spots are apparent. Bottom right, Inferior to optic nerve in left eye. Note the discrete, cream-colored spots that tend to coalesce toward the periphery.

and L.E.: 6/6 (20/20). The anterior segments were unremarkable. There was no evidence of pars planitis, but there were numerous depigmented spots throughout the fundus, as well as great numbers of vitreous cells. Fluorescein angiography of the right eye also showed cystoid maculopathy and serous detachment of the macula. A course of systemic corticosteroids was prescribed. It was difficult to determine whether the improvement was related to natural course or to therapy. She has maintained 6/6− (20/20−) visual acuity in the right eye without medications.

Case 5—A 49-year-old woman first noted decreased vision in March 1972, some 18 months before her initial visit here in August 1973. On examination, visual acuity was R.E.: 6/30+1 (20/100+1) and L.E.: 6/7.5+2 (20/25+2). The external and slit-lamp examinations of the anterior segments were unremarkable. Ophthalmoscopic examination revealed much vitreous debris in the right eye and minimal vitreous debris in the left eye. The pigmentary abnormality was diffuse and more confluent than in the other cases. The patient had been on chronic systemic corticosteroid therapy and, additionally, was given radiation therapy in September 1973. There was progressive decrease in visual acuity in the right eye to 6/120 (20/400), whereas the left eye remained 6/6 (20/20) in April 1974. On fluorescein angiography, typical diffuse retinal vascular leakage was noted throughout the fundus of the right eye.

Case 6—A 50-year-old man first noted floaters in November 1958. At the time of his visit in February 1959, there was a transient loss of temporal field in both eyes. Best corrected visual acuity was 6/4.5+ (20/15+) in both eyes. No keratic precipitates or other signs of anterior segment inflammation were noted. Particulate matter was apparent in the anterior vitreous. The maculae and disks had a minimal, but definite, edematous appearance. He exhibited the characteristic retinal pigment epithelial spots without pars plana exudate. The patient has had recurrent attacks of inflammation. As of 1973, his visual acuity remained 6/7.5 (20/25) in both eyes.

Case 7—A 53-year-old man was referred in October 1965. At that time, he noted that vision had become hazy in his right eye over the previous six months. He had congenital esotropia with an amblyopic left eye. In December 1965, visual acuity in the right eye was R.E.: 6/21−1 (20/70−1) and L.E.: 6/60 (20/200). His fundi exhibited a myriad of small, white, subretinal depigmented spots, as well as macular edema on fluorescein angiography. The patient showed no response to systemic corticosteroids or indomethacin (Indocin). As of November 1971, visual acuity had gradually decreased to R.E.: 6/21 (20/70) and L.E.: 6/60 (20/200). By July 1975, the patient's visual acuity had deteriorated to 6/60 (20/200) in both eyes. No significant change in the appearance of the fundus was noted.

Case 8—A 54-year-old woman was referred in November 1976 with bilaterally decreased vision of 16 years' duration. In 1960, she had noticed diminished color vision and a haze that was more prominent in the right eye than in the left. In 1965, visual acuity was recorded as R.E.: 6/15 (20/50) and L.E.: 6/9 (20/30). She had edema of the posterior pole, including the optic disks, and sheathing of the retinal vessels. Capillary leakage was shown with fluorescein angiography. A diagnosis of bilateral posterior uveitis was made, and the patient was treated with systemic corticosteroids for one year. She has not taken corticosteroids or any other medications for her ocular condition in the last ten years.

On ocular examination, her best visual acuity was R.E.: 6/7.5+1 (20/25+1) and L.E.: 6/9 (20/30). Results of external and slit-lamp examinations were unremarkable. Ophthalmoscopic examination revealed a typical birdshot retinochoroidopathy with a large area of depigmentation in the region of the right superotemporal vortex vein. Additionally, there was pallor of the right optic nerve head. The left eye revealed similar widespread, multiple, small spots of depigmentation. The left optic nerve head was slightly pale. Significant vitreous debris was apparent anteriorly as well as posteriorly.

Case 9—A 55-year-old man was first seen by us in October 1977 because of a history of visual acuities recorded as low as 6/30 (20/100) of two years' duration, which he equated with looking through a "fine cheesecloth." On ocular examination, best corrected visual acuity was R.E.: 6/9− (20/30−) and L.E.: 6/9− (20/30−). Results of slit-lamp examination were unremarkable. Ophthalmoscopic examination of the right eye showed the retina to be diffusely edematous, including extensive macular edema (Fig. 1, top left and right, and Fig. 2, bottom right). The pigment epithelium exhibited diffuse depigmented spots that were confluent in the posterior pole and extended in a more discrete fashion to the equator. The left eye also revealed a prominent cystoid macular edema with the appearance of a central cyst (Fig. 1, bottom left and right, and Fig. 2, top left and right and bottom left). Depigmented spots were evident in the periphery. There was no exudate over the pars plana. The patient showed some visual improvement while receiving systemic prednisone.

Case 10—A 55-year-old woman had a history of bilateral intraocular inflammatory disease since June 1972. She had received corticosteroids, including subtenon injections, but developed cataracts, which were successfully removed. Because of persistent activity of her intraocular inflammatory disease, she was referred and first examined by us in April 1978. On ocular examination, best corrected visual acuity was R.E.: 6/7.5 (20/25) and L.E.: 6/18 (20/60). External examination revealed the eyes to be white and quiet. Slit-lamp examination of the cornea revealed a few pigmented deposits, but there was no significant inflammation in the anterior segment. However, many cells in the vitreous of both eyes were evident. Ophthalmoscopic examination of the right eye showed broad, splotchy areas of depigmentation of the pigment epithelium, particularly prominent in the posterior pole and confluent with the optic nerve head, becoming more discrete in the periphery. In addition to arteriosclerotic changes,

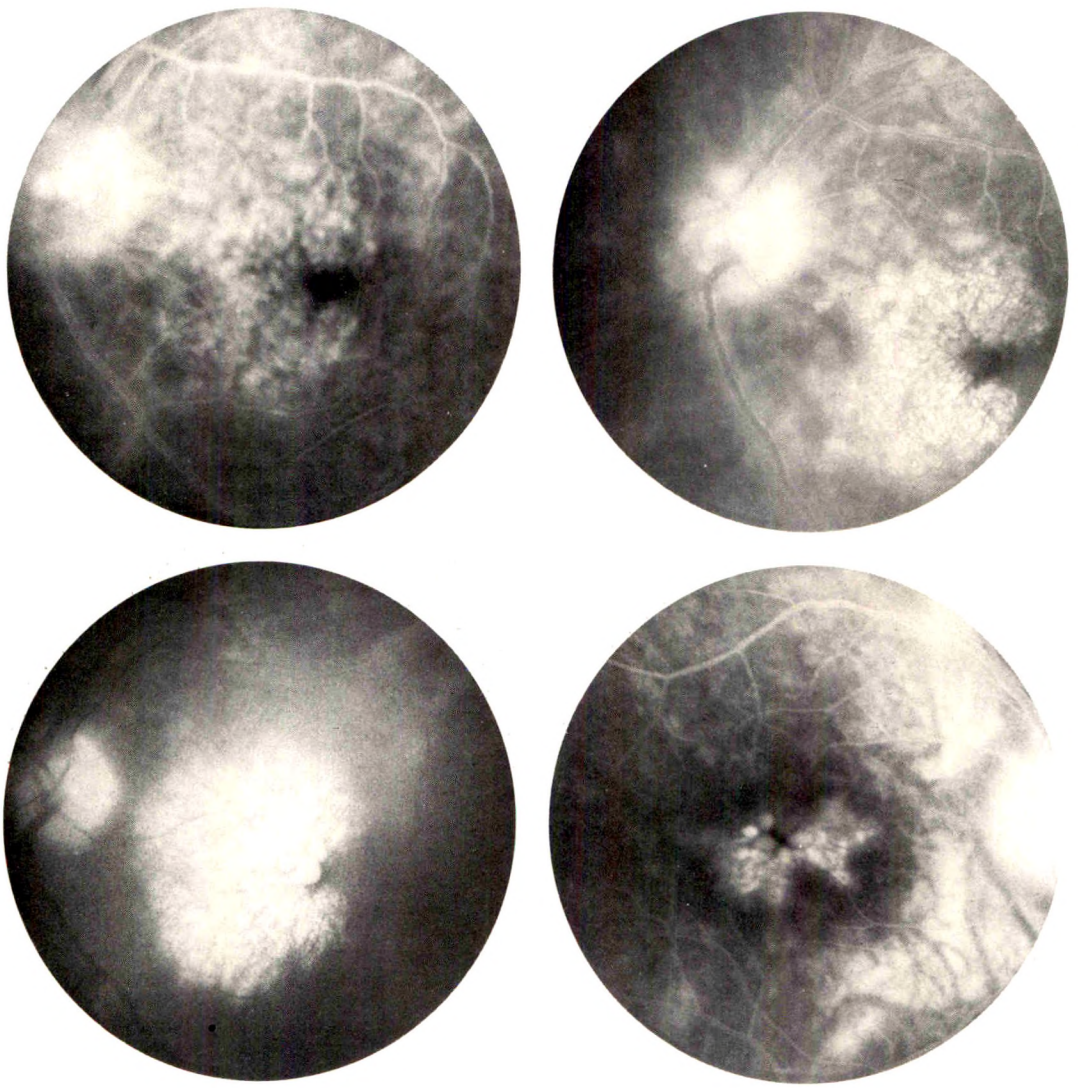

Fig. 2 (Ryan and Maumenee). (Fluorescein angiogram is of the same date and corresponds to the photographs in Figure 1.) At the time of examination and photographs, best corrected visual acuity was 6/9 (20/30) in both eyes. Top left, left eye, 61 seconds. Fluorescein leakage from the optic nerve and retinal vessels, as well as accumulation in cystoid pattern, is already apparent. Top right, left eye, 259 seconds. Note the periphlebitis with leaking and staining along the major retinal vessels. Leakage from the nerve head is prominent. Bottom left, left eye, 475 seconds. Prominent cystoid spaces throughout the papillomacular bundle as well as in the macula are filled with fluorescein. Bottom right, right eye, 455 seconds. Fluorescein fills the cystoid spaces in the macula. The cystoid maculopathy is not as extensive as that seen in the left eye (bottom left).

narrowing of the arteries was seen. There was no exudate over the pars plana. The left eye showed minimal pallor of the nerve head and identical scattered areas of centrally prominent and peripherally discrete depigmentation. Pars plana exudate was also absent. The patient returned in December 1978, at which time visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/15 (20/50).

Case 11—A 60-year-old woman came to us with an 18-month history of decreased vision in February 1977. On ocular examination, visual acuity was R.E.: 6/7.5 (20/25) and L.E.: 6/12−1 (20/40−1). One crenated, pigmented keratic precipitate in the center of the cornea of the left eye was noted. Otherwise, the anterior segments were completely normal. Ophthalmoscopic examination of the right eye showed

extensive vitreous debris. Ophthalmoscopic examination of the left eye showed the optic nerve head to be engorged, with numerous depigmented spots throughout the fundus. No deposits over the pars plana were evident, but a great amount of vitreous debris was noted, exceeding that seen in the right eye. Significant cystoid maculopathy was apparent despite the great vitreous haze. She did not show any response to corticosteroid therapy. The patient was last examined in January 1978, at which time visual acuity was R.E.: 6/7.5 (20/25) and L.E.: 6/12 (20/40) with no significant change in ocular status.

Case 12—A 60-year-old woman was referred in October 1971 with bilaterally decreased vision of at least ten years' duration. A thorough systemic medical history and examination were unrevealing. Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/120 (20/400). The eyes were white and quiet without any anterior segment signs of inflammation. There was minimal particulate matter noted in the vitreous of both eyes. Significant ocular abnormalities were limited to the ophthalmoscopic examination. There was diffuse thickening of the retina with cystoid maculopathy of both eyes, and fluorescein angiography confirmed extensive leakage and accumulation in cystoid spaces. In the left eye, a serous detachment of the sensory retina was found. The deep retinal vessels just temporal to the macula were engorged to the point of an almost telangiectatic appearance. The characteristic circumscribed, subretinal spots were subtle, but diffusely scattered throughout the fundus.

The patient was treated with 100 mg of prednisone a day and became cushingoid with a 30-pound weight gain. The corticosteroids were discontinued, and radiation to the posterior segments was administered. A total of 450 rads was given in three treatments spanning one week, after which time the serous detachment of the sensory retina subsided. Whether this was in any way causally related to the radiation therapy is not certain.

The patient has observed wide fluctuations in her vision. When last examined in January 1976, visual acuity remained R.E.: 6/9−3 (20/30−3) and L.E.: 6/60+1 (20/200+1). There has been no objective change in the results of the ophthalmoscopic examination. The fluorescein angiogram continued to show no leaking in the early phase and diffuse leaking in the late stage.

Case 13—A 67-year-old man had a four-year history of gradually decreasing vision in the left eye. On ocular examination in November 1971, visual acuity in the right eye was 6/6 (20/20) and results of the examination were normal. By contrast, visual acuity in the left eye was 6/30 (20/100) with small, particulate vitreous opacities and diffuse birdshot retinochoroidopathy, especially inferiorly. Marked cystoid maculopathy and prominent sheathing of vessels, particularly of the large veins, were noted on fluorescein angiography, as well as pale, diffuse edema with profuse leakage of fluorescein from the optic nerve head. Systemic corticosteroid therapy (60 mg of prednisone a day) was prescribed through May 1972, at which time visual acuity improved to 6/9 (20/30). The prednisone was then discontinued. When visual acuity dropped back to 6/15 (20/50) in September 1972, systemic corticosteroid therapy was again prescribed. Visual acuity improved in December 1972 to 6/6 (20/20) in the left eye. Corticosteroid therapy was tapered and then discontinued with maintenance of 6/6 (20/20) visual acuity in both eyes. This case is of interest because of the strict unilaterality of the condition and the uncharacteristic response to systemic corticosteroid therapy.

Results

The length of follow-up in our 13 cases (Table) of birdshot retinochoroidopathy ranged from zero to 23 years. The mean follow-up for the entire group was 8.5 years, and the median was 10 years. At the time of their initial examination by us, the mean age of the group was 50.3 years, and the median age was 53 years, with a range from 35 to 67 years.

All 13 patients showed the spectrum of retinal pigment epithelial-choroidal changes referred to as birdshot depigmentation. Vitreous opacities were also present in all 13 cases. However, only four patients showed significant anterior segment signs of inflammation, whereas nine had normal anterior segments without ray and cell or keratic precipitates. The presence of macular edema was confirmed in seven cases (Cases 3-5, 7, 9, 11, and 12) and could not be ruled out in the remaining six cases. The optic nerve head showed signs of disk edema and leakage in seven cases (Cases 5-9, 11, and 13). Two patients (Cases 1 and 2) developed optic atrophy, despite previously normal optic nerve heads.

The condition tends to be bilateral and symmetrical. A full-blown condition with marked bilateral decrease in visual acuity [6/60 (20/200) or less] was noted in three patients (Cases 1, 2, and 7). Six patients had symmetrical, but only minimal to moderate involvement, with a slight decrease in visual acuity in both eyes (Cases 3, 6, and 8-11). There was asymmetric involvement, with marked visual loss in one eye (6/60 [20/200] or less) and only minimal to moderate disturbance of the

TABLE

SUMMARY OF CASES WITH BIRDSHOT RETINOCHOROIDOPATHY*

Case No.,	Age (yrs),	Sex	History	Initial Visual Acuity R.E.	Initial Visual Acuity L.E.	Anterior Segment	Vitreous	Pigment Epithelium and Choroid
1,	35,	F	Decreased vision and uveitis, three years	6/21 (20/70)	6/60 (20/200)	Normal	Cells	Numerous depigmented spots
2,	36,	F	L.E.: Hazy vision, eight months	6/4.5 (20/15)	6/7.5 (20/25)	Few crenated keratic precipitates	Debris	Diffuse leakage on fluorescein, depigmented fundus
3,	37,	F	Decreased vision, four years	6/6− (20/20−)	6/7.5+ (20/25+)	Normal	Debris	Numerous depigmented spots
4,	42,	F	R.E.: Decreased vision, four months	6/15 (20/50)	6/6 (20/20)	Normal	R.E.: Opacities	R.E.: Numerous depigmented spots, "moth eaten," particularly above and below; serous detachments
5,	49,	F	R.E.: Decreased vision, one year	6/30+ (20/100+)	6/7.5+ (20/25+)	Normal	R.E.: Debris and opacities L.E.: Debris	R.E.: Mottled depigmentation, particularly around the optic nerve L.E.: Similar depigmentation, especially nasally

TABLE

SUMMARY OF CASES WITH BIRDSHOT RETINOCHOROIDOPATHY*

Retina	Optic Nerve	Course	Systemic Diseases and Association	Final Visual Acuity R.E.	Final Visual Acuity L.E.	Follow-up (yrs)
L.E.: Extensive serous detachment	Subsequent optic atrophy	Narrowing of vessels and optic atrophy led to 6/240 visual acuity	None	(5/200)	6/140 (7/200)	23
Dilated vessels	Subsequent optic atrophy	Treatment: Prednisone 12/65: Leak along superior and inferior temporal vessels; visual acuity: R.E.: 6/9 (20/30), L.E.: 6/12 (20/40) 12/69: Large macular cyst, long-standing vitritis 4/71: Visual acuity R.E.: 6/7.5 (20/25), L.E.: counting fingers 1/72: x-ray 450 rads total 1/74: Visual acuity R.E.: 6/24 (20/80), L.E.: counting fingers; R.E.: posterior subcapsular cataract, large serous detachment 4/76: Visual acuity R.E.: 6/60 (20/200), L.E.: counting fingers; cystoid changes in over lying retina	Increased white blood cell count 11 to 20,000 mm^3	6/60 (20/200)	Counting fingers	12
L.E.: Cystoid maculopathy	Normal	No significant response to corticosteroids	None	6/6 (20/20)	6/7.5+ (20/25+)	0
R.E.: Cystoid maculopathy	Normal	12/68: Prednisone 20 mg/day/six weeks; INH, 18 months; "Inactive uveitis" 6/74: Off medications	Positive second strength PPD	6/6− (20/20−)	6/6 (20/20)	7
R.E.: Diffuse leakage and signs of vasculitis	Minimal engorgement	3/73: Long-term corticosteroids begun 8/73: Radiation, total dose 600 rads 10/73: Visual acuity: R.E.: 6/18+ (20/60+), L.E.: 6/4.5 (20/15); slightly less inflammatory response; R.E.: Diffuse leakage along inferior temporal vessels, "vasculitis" 4/74: Visual acuity: R.E.: 6/120 (20/400), L.E.: 6/6 (20/20)	Polymyalgia rheumatica Temporal artery biopsies negative	6/120 (20/400)	6/6 (20/20)	4

Table continued on following pages

TABLE *(Continued)*

SUMMARY OF CASES WITH BIRDSHOT RETINOCHOROIDOPATHY*

Case No.,	Age (yrs)	Sex	History	Initial Visual Acuity R.E.	Initial Visual Acuity L.E.	Anterior Segment	Vitreous	Pigment Epithelium and Choroid
6,	50,	M	"Unclear vision," 1½ years	6/4.5+ (20/15+)	6/4.5+ (20/15+)	Normal	Debris and opacities	R.E.: Mild atrophic area inferior to disk L.E.: Depigmentation around disk
7,	53,	M	R.E.: Deteriorating vision, six months	6/21− (20/70−)	6/60 (20/200)	Fine to medium keratic precipitates and ray	Opacities	Diffuse birdshot
8,	54,	F	1960: Hazy vision, R.E. more than L.E. 1965: Bilateral macular uveitis	6/7.5+ (20/25+)	6/9 (20/30)	Normal	Opacities	Diffuse birdshot
9,	55,	M	Decreased vision Vitreous debris	6/9− (20/30−)	6/9− (20/30−)	Normal	Opacities	L.E.: Diffuse birdshot, more marked in the posterior pole
10,	55,	F	Bilateral intraocular inflammatory disease, four years; corticosteroid treatment	6/7.5 (20/25)	6/18 (20/60)	Normal	Opacities	R.E.: Broad, splotchy depigmented areas L.E.: Minimal pallor of nerve head; prominent discrete depigmented areas in the periphery
11,	60,	F	Decreased vision, 18 months	6/7.5 (20/25)	6/12− (20/40−)	L.E.: One keratic precipitate	Opacities	Diffuse but subtle infiltration with depigmented spots
12,	60,	F	Decreased vision 13 years	6/6 (20/20)	6/120 (20/400)	Normal	Opacities	Diffuse but subtle infiltration

TABLE *(Continued)*

SUMMARY OF CASES WITH BIRDSHOT RETINOCHOROIDOPATHY*

Retina	Optic Nerve	Course	Systemic Diseases and Association	Final Visual Acuity R.E.	Final Visual Acuity L.E.	Follow-up (yrs)
Edematous maculae L.E.: "Flame-shaped" hemoglobin	Edematous disks	1961: Visual acuity: R.E.: 6/60 (20/200), L.E.: 6/30 (20/100); responded to corticosteroids, intermittent recurrent attacks of inflammation 1973: Visual acuity: R.E.: 6/7.5 (20/25), L.E.: 6/7.5 (20/25)	None	6/7.5 (20/25)	6/7.5 (20/25)	13
Cystoid maculopathy 2/69: R.E.: Narrow vessels, "granular" macula	Fluorescein leakage above and below disk	Treatment: indomethacin (Indocin) 25 mg three times a day 2/66: Visual acuity: R.E.: 6/15+ (20/50+) 2/67: L.E.: Transconjunctival cry over pars plana 11/71: Visual acuity: R.E.: 6/21 (20/70), L.E.: 6/60 (20/200)	None	6/60 (20/200)	6/60 (20/200)	10
Vascular sheathing and edema	Slight pallor; fluorescein leakage	Treatment: Prednisone, 60 mg/day/one year; vision stable off medicine for 11 years	None	6/7.5+ (20/25+)	6/9 (20/30)	16
R.E.: Edema and cystoid maculopathy	Normal	Improvement of visual acuity of R.E.: 6/30 (20/100) L.E.: 6/30 (20/100)	None	6/9 (20/30)	6/9 (20/30)	0
No gross abnormality	L.E.: Minimal pallor	Pigment epithelial change continues, but no active disease at present	Unknown	6/9 (20/30)	6/15 (20/50)	1/2
L.E.: Cystoid maculopathy	Swollen	Cystoid maculopathy of the left eye	Unknown	6/7.5 (20/25)	6/12 (20/40)	1
L.E.: Cystoid maculopathy; dilation of deep perifoveal capillary network	Small disks	1/73: Visual acuity: R.E.: 6/6 (20/20), L.E.: 6/30 (20/100) 10/73: Visual acuity: R.E.: 6/7.5 (20/25), L.E.: 6/60 (20/200) Large serous detachment of sensory retina occurred; recurrent episodes of inflammation developed with wide fluctuation of visual acuity	Normal	6/9− (20/30−)	6/60+ (20/200+)	18

Table continued on following pages

TABLE *(Continued)*

SUMMARY OF CASES WITH BIRDSHOT RETINOCHOROIDOPATHY*

Case No.,	Age (yrs)	Sex	History	Initial Visual Acuity R.E.	Initial Visual Acuity L.E.	Anterior Segment	Vitreous	Pigment Epithelium and Choroid
13,	67,	M	Decreased vision, four years	6/6 (20/20)	6/30 (20/100)	Normal	L.E.: Debris	L.E.: Diffuse birdshot, particularly inferiorly

*INH indicates isonicotine hyrdrazine; PPD, purified protein derivative of tuberculin.

other eye, in two cases (Cases 5 and 12). The condition was unilateral in two cases (Cases 4 and 13).

These 13 patients were treated with a variety of nonspecific anti-inflammatory regimens, which included systemic corticosteroids (prednisone), indomethacin (Indocin), radiation therapy, and even antimetabolites. Only two cases (Cases 6 and 13) seemed to show a good response to corticosteroid therapy. Six patients maintained relatively good vision, but the role of corticosteroids does not seem nearly so clear in them (Cases 3, 4, and 8-11). In five of the 13 patients, visual acuity was reduced to 6/60 (20/200) or less in at least one eye each (Cases 1, 2, 5, 7, and 12).

DISCUSSION

Maumenee[1] has enumerated the arguments for describing a new syndrome in intraocular inflammation. An excellent example of the importance of precise clinical description of unfamiliar entities in the absence of a clear cause has been provided by Gass,[11] who initially grouped a new syndrome embracing optic atrophy, pigment epithelial disturbance, and retinal vascular attenuation under the heading of "unilateral wipeout syndrome." Subsequent histopathologic correlation of one eye in the late stage of this condition[12] and additional new observations of early-phase cases have permitted incrimination of *Toxocara canis* as the most probable causal agent for what Gass and associates[13] now formally designate as diffuse unilateral subacute neuroretinitis. It is by excellent clinical description and scrupulous documentation of all aspects of an unfamiliar entity that accurate causal explanation becomes possible.

It has been difficult to choose an appropriate name for this entity in the absence of cause and understanding of its pathogenesis. Other terms that have been considered in addition to birdshot retinochoroidopathy include: diffuse capillary vasculopathy, diffuse angiopathy, diffuse

TABLE *(Continued)*

SUMMARY OF CASES WITH BIRDSHOT RETINOCHOROIDOPATHY*

Retina	Optic Nerve	Course	Systemic Diseases and Association	Final Visual Acuity R.E.	Final Visual Acuity L.E.	Follow-up (yrs)
L.E.: Sheathing of vessels	L.E.: Pale	Treatment: Prednisone 1/72: Visual acuity: R.E.: 6/6 (20/20), L.E.: 6/15 (20/50) 5/72: Visual acuity: R.E.: 6/6 (20/20), L.E.: 6/9 (20/30) 9/72: Stop prednisone prescribed again; Visual acuity: R.E.: 6/6 (20/20), L.E.: 6/15 (20/50) 12/72: prednisone; Visual acuity: R.E.: 6/6 (20/20), L.E.: 6/6 (20/20)	Hypertensive (205/95 mm Hg) ischemic heart disease	6/6 (20/20)	6/6 (20/20)	6

chorioretinal vasculitis, and diffuse retinochoroidocapillopathy. All of these terms are either so long that they would never be used or so brief that they are not accurate. The lack of an exact understanding of the pathogenesis, in part, underlies the problems in terminology. The main reason for using birdshot retinochoroidopathy as a term for this entity is that this descriptive clinical picture does not imply a specific pathogenesis as would the alternatives mentioned above. Thus, when the pathogenesis has been elucidated, a more exact name can be applied rather than changing a pre-existent name with an implied pathogenesis.

Thorough systemic uveitis surveys have failed to reveal any causal agent or pathogenetic mechanism. This entity in intraocular inflammation is characterized by profuse leakage from the retinal capillaries. The similarities with the pars planitis syndrome have been emphasized in the description, that is, a quiet eye with minimal anterior segment inflammation but prominent retinal vascular leakage and vitreous debris. However, there was no pars plana exudate in any of the birdshot cases, and we have never seen the characteristic depigmented spots of pars planitis, despite the long follow-up of both groups of cases. Senile vitritis, as described by Gass,[14] is also typified by retinal vascular leakage and vitreous debris in the absence of pars plana exudate. However, none of the cases with senile vitritis have been described to have these characteristic spots. These depigmented spots may be related to the previous accumulation of fluid, more likely beneath the sensory retina than beneath the retinal pigment epithelium, or to inflammatory foci in the choroid or the retinal pigment epithelium. Differential diagnosis may also include other inflammatory disorders such as Harada's syndrome, Behçet's disease, geographic choroidopathy, or acute posterior multifocal placoid pigment epitheliopathy.

Harada's syndrome usually occurs in

more darkly pigmented individuals and has many systemic associations in addition to the characteristic exudative retinal detachments. It is not primarily a disease affecting the retinal capillaries and thus does not exhibit the characteristic leakage and cystoid macular edema seen in our patients. While Behçet's disease shows intraocular inflammation, it exhibits severe progression and more prominent anterior segment signs, including hypopyon. Its systemic associations should readily differentiate Behçet's disease from birdshot, in which we found no extraocular complications. Geographic choroidopathy is a relentless condition characterized by inflammation and steady progression at the level of the retinal pigment epithelium. Acute posterior multifocal placoid pigment epitheliopathy is a disorder limited to the level of the pigment epithelium or the superficial choroid and characterized by a good prognosis for visual recovery. The changes and areas of abnormal choroidal filling with subsequent staining are different from the pigmented birdshot spots in this entity, which behave initially as a window defect with late staining in keeping with a disorder at the level of the pigment epithelium. The course is much different in that the birdshot seems to be more relentless with visual loss on the basis of cystoid maculopathy, whereas acute posterior multifocal placoid pigment epitheliopathy has a more rapid course and resolution.

Birdshot retinochoroidopathy is a disease with many manifestations and a broad spectrum, as noted in the case histories and results. The mechanism of decreased visual acuity may be optic atrophy, as in Cases 1 and 2, with attenuation of the arteries. There may also be persistent cystoid macular edema, as documented in seven cases (Cases 3, 4, 6, 7, 9, 11, and 12). As an entity in intraocular inflammation, it is not surprising that nonspecific therapy, such as systemic corticosteroids, was not effective. Only two cases (Cases 6 and 13) seemed to show a definitive response to corticosteroid therapy. By contrast, Smith, Godfrey, and Kimura[8] noted 73% of their pars planitis patients to maintain good vision after a follow-up of 12 years. In our group, five of the 13 patients with follow-up showed 6/60 (20/200) or less visual acuity over the course of a 12-year follow-up. The limitations of the small group of cases reported and the possible bias of ascertainment in this referral practice make it impossible to generalize as to the course of these cases regarding prognosis.

Summary

Thirteen patients had a new syndrome and entity in intraocular inflammation called birdshot retinochoroidopathy, which was characterized by a white, painless eye with minimal anterior segment inflammation but particulate debris in the anterior and posterior vitreous. There was profuse retinal vascular leakage with resultant retinal, macular, and disk edema, which are the primary causes of the decreased vision in this syndrome. Long-term follow-up (mean of ten years) revealed that only two patients seemed to respond to anti-inflammatory therapy (systemic corticosteroids) and five patients progressed to 6/60 (20/200) or less visual acuity in at least one eye.

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KERATOPATHY AFTER ORAL ADMINISTRATION OF TILORONE HYDROCHLORIDE

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Tilorone HCl (2,7-bis [2 diethlamino-ethoxy] fluoren-9-one dihydrochloride) produces many biological effects in laboratory animals. The drug possesses antitumor[1–4] and antiviral activity[5–8] and is anti-inflammatory.[9] The immunologic effects of tilorone HCl include interferon induction,[5,7,8] stimulation of 19s antibody production[10,11] and phagocytosis.[1,2,4] Although it stimulates B lymphocytes, it inhibits T cells.[12] Because of its potential antitumor effects in man, the drug is being investigated in the treatment of neoplasms.[13,14] We report the clinical and histopathologic ocular changes in patients given tilorone orally.

CASE REPORTS

Case 1—A 52-year-old woman[15] with a renal transplant and progressive multifocal leukoencephalopathy was taking 750 mg (2.5 mg/kg) of tilorone HCl twice weekly. Though asymptomatic, the patient underwent a routine ophthalmic examination three months later. Visual acuity at this time was 6/6 (20/20) in each eye and the examination was unremarkable except for the presence of diffuse white subepithelial opacities bilaterally, covering the entire cornea, as seen with a biomicroscope. Because of the tendency of progressive multifocal leukoencephalopathy to occur in immunosuppressed states and two previous episodes of threatened renal graft rejection, she continued to take the medication. The patient was followed up every six weeks for the next five months. During this time, the corneal clouding developed into a prominent whorl pattern (Fig. 1), visible without the aid of a biomicroscope. Corneal sensation was unaffected. A conjunctival and lamellar corneal biopsy was done.

Fig. 1 (Weiss, Weinberg, and Regelson). Diffuse subepithelial whorl pattern and clouding of cornea.

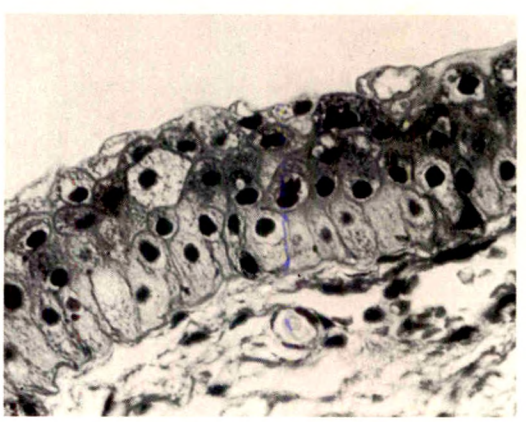

Fig. 2 (Weiss, Weinberg, and Regelson). Cloudy swelling and cytoplasmic inclusions in conjunctival epithelium (hematoxylin and eosin, ×800).

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Giemsa stain of the conjunctival scraping and hematoxylin and eosin stain of the conjunctival and corneal biopsy specimens showed cloudy swelling of the epithelium and cytoplasmic inclusions (Fig. 2). Feulgen negative basophilic cytoplasmic inclusions were also present, more prominent in the corneal than the conjunctival epithelium. The corneal stroma was normal. Transmission electron microscopy revealed the presence of myelinoid bodies, which are phospholipid-rich single-membrane bound structures containing whorls of electron-dense membranes (Figs. 3 and 4).[16] Wright stain and electron microscopy of peripheral blood smear revealed similar inclusions in the lymphocytes (Fig. 5). Gas chromatographic and mass spectrophotometric analysis of the conjunctival and corneal biopsy specimens revealed tilorone HCl concentrations of 120 and 400 ppm, respectively. A buccal mucosa smear was normal. Three days after the lamellar corneal biopsy the wound had re-epithelialized, with return of the whorl-like subepithelial opacity. The drug was discontinued 31 months after starting the tilorone. Three months later the patient denied any ophthalmic complaints, visual acuity remained at 6/6 (20/20), and corneal examination revealed a slow resolution of the opacities.

Case 2—A 34-year-old woman with mycosis fungoides came here before she started taking a tilorone HCl regimen of 250 mg (8.1 mg/kg of body weight) twice daily. At the time of this examination, she denied any ophthalmic complaints. Visual acuity

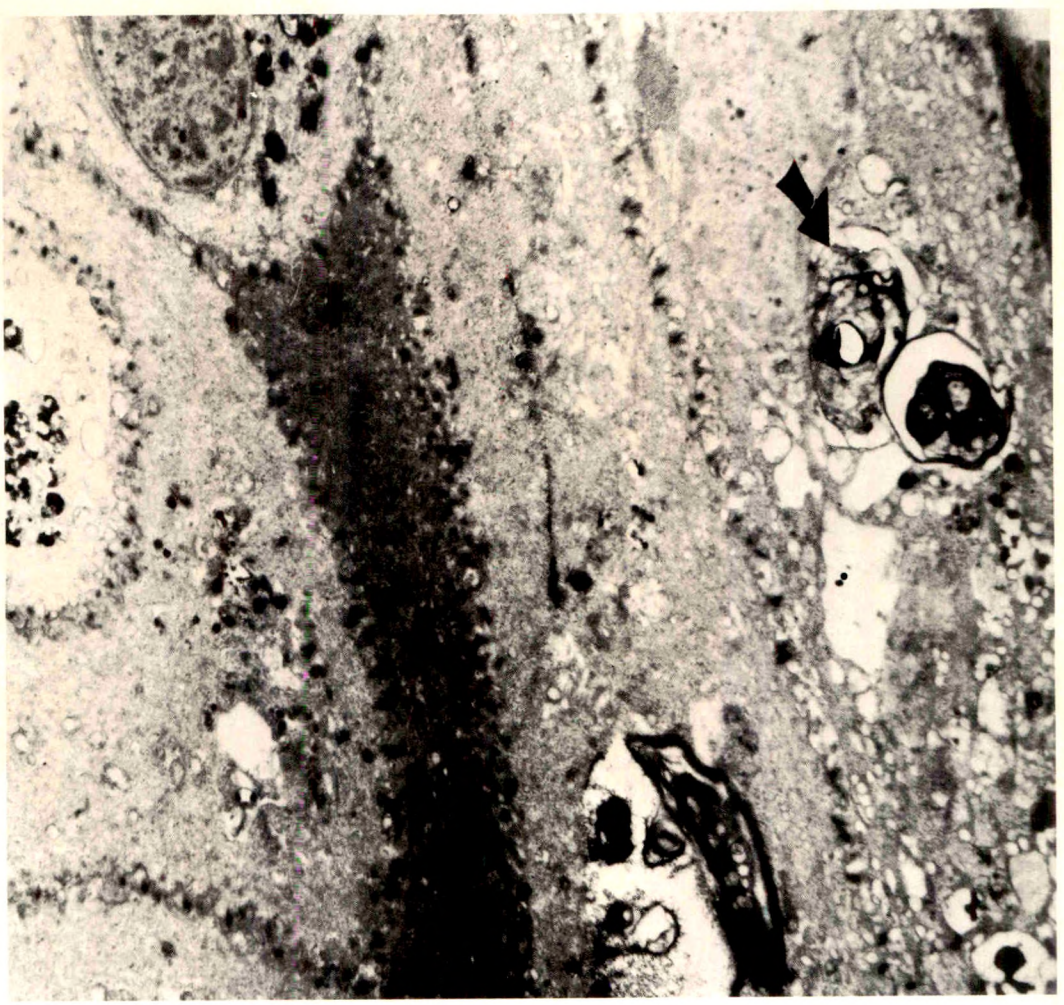

Fig. 3 (Weiss, Weinberg, and Regelson). Cornea. Extensive degenerative changes are present in the corneal epithelium including myelinoid bodies (arrow) (×7,500).

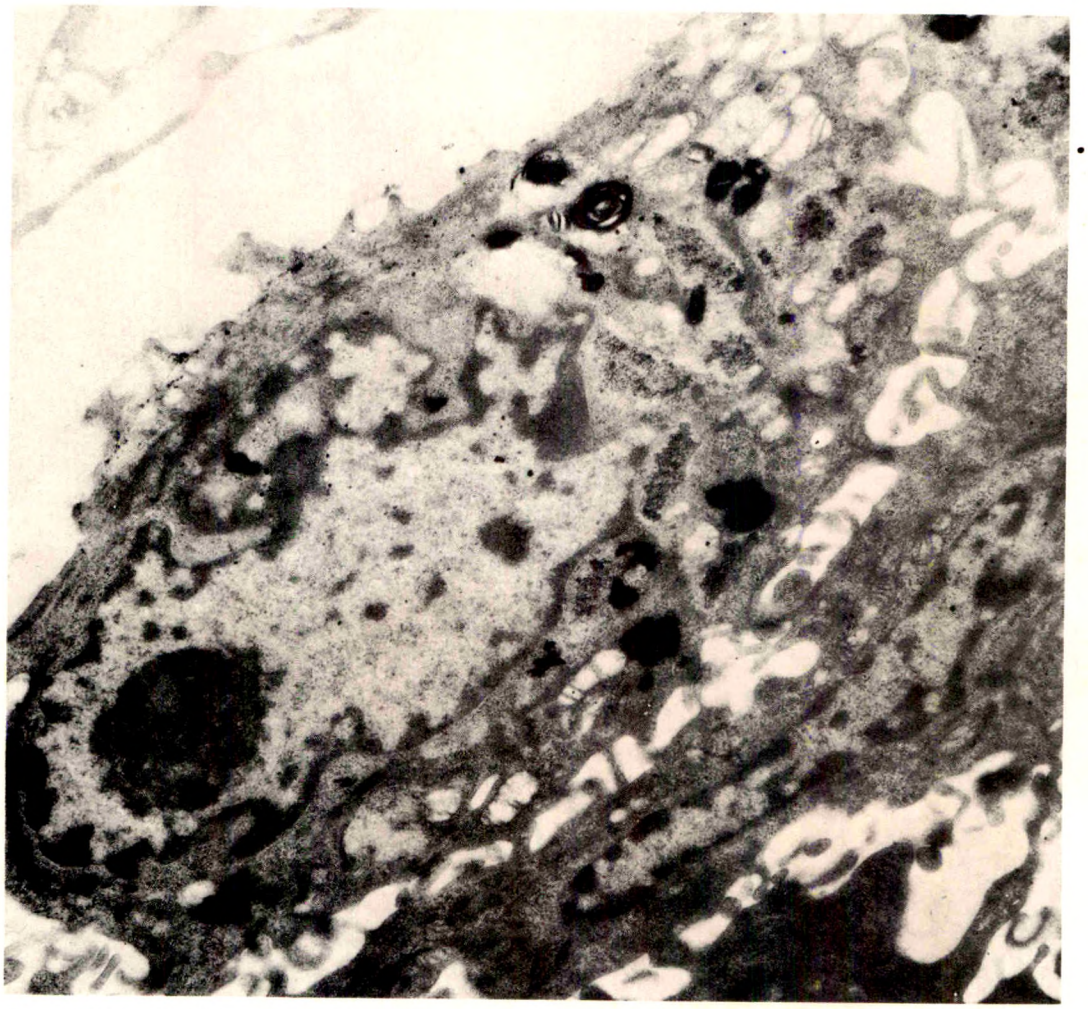

Fig. 4 (Weiss, Weinberg, and Regelson). Conjunctiva. Myelinoid bodies in the epithelium (×15,000).

was 6/6 (20/20) in both eyes. Results of tonometry, biomicroscopic and ophthalmic examination, color vision, and Goldmann perimetry were all normal.

The patient was next examined two months later. She complained of blurred vision at near and far for 20 to 30 minutes after taking each dose of tilorone HCl as well as the presence of blue halos around point light sources. Visual acuity was again 6/6 (20/20) and J1+ in both eyes. Results of the remainder of the ophthalmic examination were normal except for a subtle clouding of the epithelium and anterior stroma seen with the biomicroscope. In consultation with the dermatologist who was treating the patient, the decision was made to decrease the dose of tilorone HCl to 250 mg (4.1 mg/kg of body weight) daily. The patient was re-examined one month later. At this time the cutaneous lesions of mycosis fungoides, which on the larger dose of tilorone HCl were regressing, had stabilized. The patient now denied the previous ocular complaints. Results of ocular examination showed no change from that of two months previously. At this point the medication was discontinued. The patient was re-examined in one month. Though she again denied any ophthalmic complaint, the results of the corneal examination were unchanged. However, the skin lesions had enlarged. The dosage of tilorone HCl was increased to 250 mg twice daily and the patient was re-examined one month later. At this time the blurred vision and blue halos had returned. Biomicroscopic examination revealed an increase in the density of the subepithelial opacities. Hematoxylin and eosin stain and electron microscopy (Figs. 6 and 7) of a conjunctival biopsy showed the

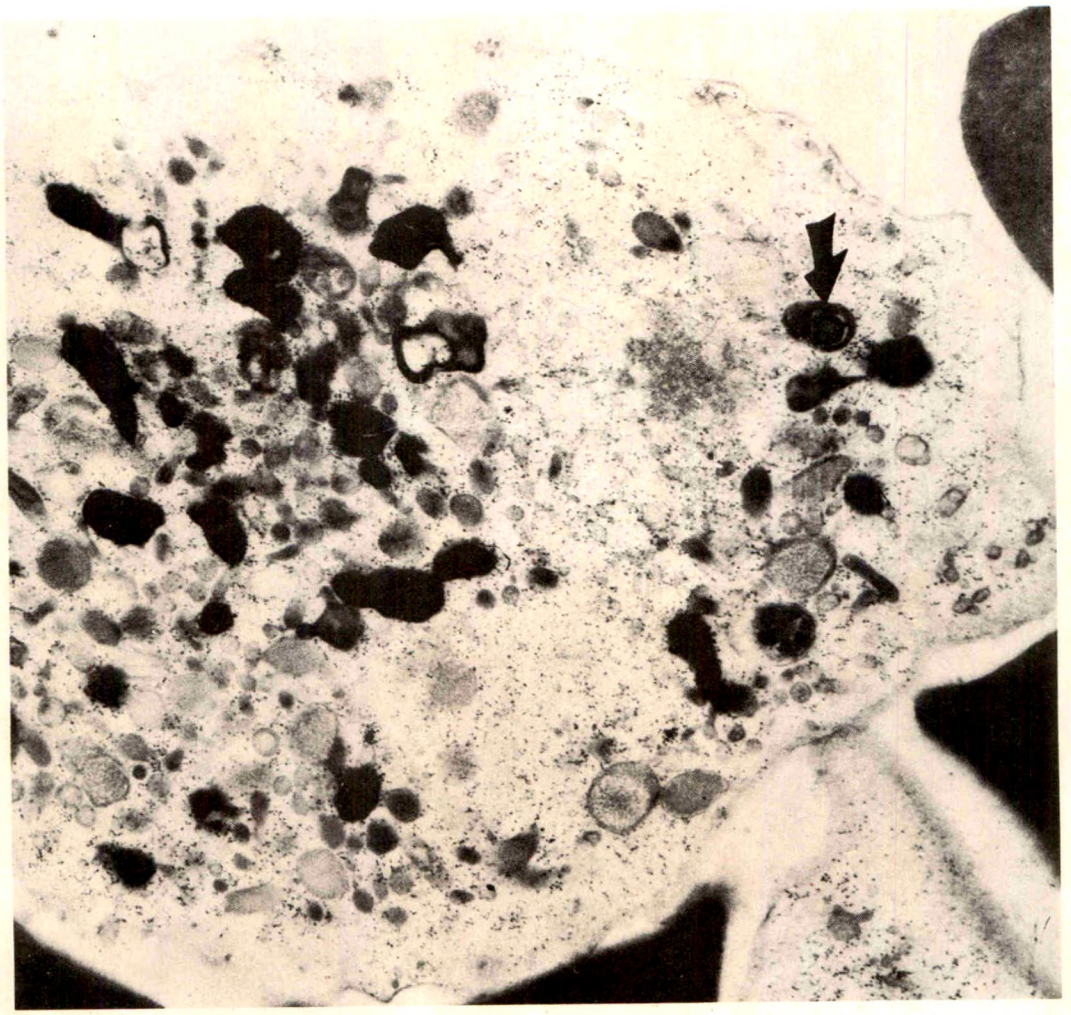

Fig. 5 (Weiss, Weinberg, and Regelson). Polymorphonuclear leukocyte from peripheral blood showing myelinoid bodies (arrow) and other dense osmiophilic structures (×24,000).

same findings as in Case 1. The dosage schedule was changed to 750 mg twice weekly and the patient is being followed up every month.

The following patients participated in a study of the antitumor effects of tilorone at the Medical College of Virginia in 1974.[5]

Case 3—A 64-year-old man with lymphosarcoma was given a regimen of 750 mg (8.4 mg/kg of body weight) of tilorone HCl daily for ten days, followed by three weeks without therapy. On the third and fourth course of therapy the dosage was reduced to 500 mg/day because of nausea. During the fourth course, also at the reduced dosage, the patient complained of visual disturbances, with colored rings in the periphery of his visual fields, and trouble focusing when reading. On ophthalmic examination, visual acuity was correctible to 6/6 (20/20) in both eyes. Biomicroscopic examination of each cornea revealed a whorl-like clouding of the epithelium. Results of the remainder of the examination, including visual fields, were normal. At this time tilorone HCl was discontinued. The patient was not re-examined until approximately one year later, at which time he denied any visual complaints and biomicroscopic examination failed to reveal the above findings.

Case 4—A 40-year-old woman with metastatic melanoma, was given a continuous dosage of

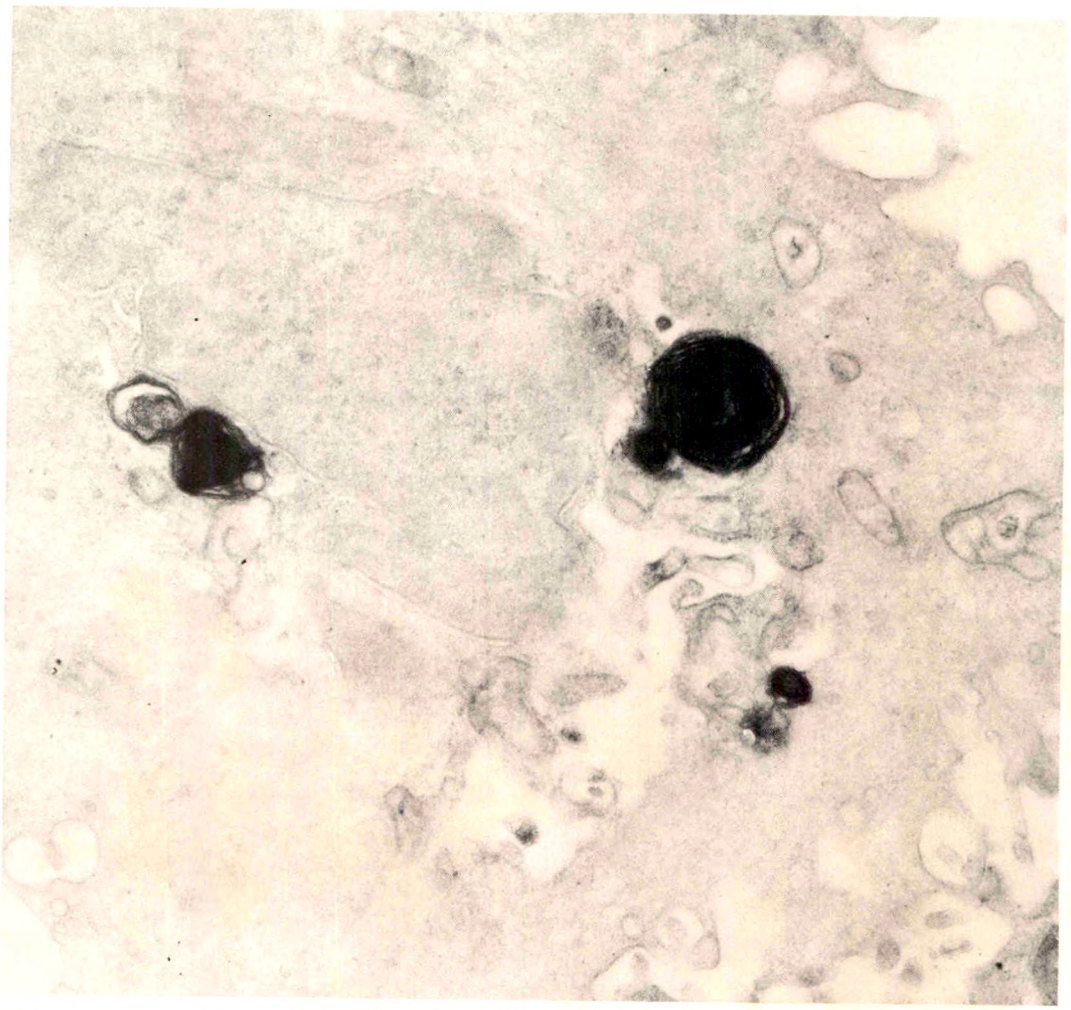

Fig. 6 (Weiss, Weinberg, and Regelson). Conjunctiva. Well-formed myelinoid bodies in the epithelium (×20,000).

250 mg (4.2 mg/kg of body weight) of tilorone HCl twice daily. Approximately three months later she complained of blue halos surrounding lights at night. She consulted with her family ophthalmologist who was able to elicit symptoms even in daylight. Visual acuity was 6/6 (20/20) in each eye and the results of the ophthalmic examination were normal with the exception of the corneal findings. The epithelium and anterior stroma regions revealed a diffuse, subtle clouding, extending from corneoscleral limbus to corneoscleral limbus, symmetrical in both eyes. This opacification was of radial configuration appearing to emanate from the center of the cornea. There was no fluorescein staining of the epithelium. The tilorone HCl was then discontinued and the patient was lost to follow-up.

Case 5—A 55-year-old man with lymphocytic lymphosarcoma began taking 500 mg (7.4 mg/kg of body weight) of tilorone HCl daily. Symptoms of depression and lethargy caused a dose reduction to 250 mg (3.7 mg/kg of body weight) daily. This dose was maintained for three months. The patient had no visual complaints, but because of the previously reported cases an ophthalmologic consultation was obtained. Again, a diffuse epithelial and subepithelial corneal haze composed of white deposits was seen in both eyes. The findings were more prominent in the left eye, which showed radiation zones. There was also a large crystalline deposit at the 3 and 9 o'clock positions in the perilimbal conjunctival regions. Results of the remainder of the ocular examination were normal. The patient was followed

Fig. 7 (Weiss, Weinberg, and Regelson). Case 1. Conjunctival blood vessel showing myelinoid bodies in the endothelium (arrow). Similar structures were seen in the conjunctival vessel (×30,000).

up for several months since the discontinuance of the drug with a total resolution of the conjunctival and corneal findings in approximately five months.

Discussion

Tilorone HCl, an experimental antitumor drug, is being evaluated at the Medical College of Virginia. Two patients receiving the drug at doses of 2.5 and 8.1 mg/kg of body weight for one year and two months respectively, showed the appearance of corneal opacities. Tilorone HCl was histochemically shown to be present in the conjunctival and corneal biopsy specimens in Case 1. Additionally, three patients of 14 studied, who received doses of 4.2 to 8.4 mg/kg of body weight and from 62 to 105 days after the start of therapy, complained of halos around pinpoint light sources that were associated with similar corneal findings. The development of the findings appears related to the total amount of tilorone HCl received.

Kaufman and associates[17] showed that eyes of rabbits instilled with tilorone HCl developed no pathologic changes. Topical administration of this drug in human volunteers produced a corneal epithelial change similar to minimal corneal edema, first visible about ten days after treatment began. From biomicroscopic examination Kaufman and associates concluded that this change consisted of a fine amount of drug stored in the corneal epithelium. No deposits were noted in the stroma or endothelium and the results of the remainder of the ophthalmic examination were normal. The epithelial deposits were accompanied by blurred vision and halos around light unassociated with decrease in visual acuity. Approximately two months were required for the biomicroscopic findings and symptoms to disappear.

The corneal lesions produced by tilorone HCl are white epithelial and subepithelial opacities. They are often arranged in a curvilinear pattern, forming a fan or whorl, which does not disturb the surface epithelium and produces no discomfort.

Several other pharmacologic agents have produced corneal lesions when given continuously. Of importance is the drug chloroquine,[18,19] which produces similar corneal changes as tilorone HCl, but additionally produces retinopathy. Chloroquine has also been found to produce myelinoid bodies,[20] but unlike tilorone HCl, affects corneal sensation and some of the induced changes are not reversible.

Quinacrine[18] is another antimalarial that produces corneal lesions similar to those found with chloroquine. Those persons exposed to quinacrine in its manufacture have complained of seeing blue halos or multicolored rings and lights that have been attributed to the corneal deposits.

Systemically administered quinacrine commonly colors the skin yellow. It is tempting to assume that tilorone HCl would also concentrate in the epidermis. This may account for the initial resolution of skin lesions in Case 2.

As tilorone HCl is probably absorbed by many tissuses, the ophthalmic manifestations serve as an indication of the drug's storage and potential damage elsewhere in the body. This may easily be determined by biomicroscopic and conjunctival cytologic examination.

Tilorone HCl has been found to induce reversible ocular changes characterized by corneal opacities. It is important to note these effects as tilorone HCl may have a clinical place in immunoadjuvant control of tumor growth as well as a possible role in control of host-graft rejection.

Summary

Two patients given tilorone HCl orally for varying periods of time had clinical and histopathologic ocular changes. Retrospective study of 14 cancer patients who were taking tilorone HCl orally revealed that three patients had similar ophthalmic findings accompanied by the appearance of blue halos around pinpoint light sources. Examination revealed a diffuse clouding of the epithelium sometimes associated with subepithelial infiltrates. Abnormalities seen histologically included cloudy swelling of the epithelium and cytoplasmic inclusions. By electron microscopy these were found to be myelinoid bodies. Gas chromatography and mass spectrophotometry showed that tilorone HCl was present in the cornea and conjunctiva. Visual acuity was not affected and these changes were slowly reversible with the cessation of therapy.

Biomicroscopic and conjunctival cytologic examination may serve to indicate the drug's storage and potential damage in the body.

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HLA ANTIGENS IN RECURRENT STROMAL HERPES SIMPLEX VIRUS KERATITIS

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The fundamental biologic significance of the HLA histocompatibility complex is the association of its gene product with human disease.[1] The evidence for HLA and disease and association and predisposition to recurrent virus infection is limited. There have been two conflicting reports on the association of HLA and recurrent herpes simplex virus infection.[2,3] Russell and Schlaut[2] reported an increased prevalence of HLA-A1 in patients with recurrent herpes simplex virus labialis. Zimmerman and associates[3] found significant increases in HLA-B5 in recurrent epithelial herpes keratitis. However, only the HLA-A and -B specificities were determined in these reports. Because typing for the HLA-C and -DR (B lymphocyte allo-antigen) specificities have recently become available, we studied the possible relationship between HLA-A, -B, -C, and -DR antigens with predisposition to recurrent herpes stromal keratitis. HLA-D locus was first defined by the use of homozygous typing cells using the mixed lymphocyte cytotoxicity reaction. These specificities can now be determined serologically by using B lymphocytes. The antigens identified on B lymphocytes by the cytotoxicity reaction are the antigens of the DR locus.[4] The DR may be the same as the D locus with 99% perfect concordance.

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SUBJECTS AND METHODS

Forty-eight patients with a history of recurrent herpes stromal keratitis were studied. All patients were examined at the External Disease Clinic of the Jules Stein Eye Institute, UCLA School of Medicine, and at the Corneal-External Disease Clinic of the Department of Ophthalmology, Vanderbilt University School of Medicine. Typing for 15 HLA-A, 24 HLA-B, and four HLA-C antigens was performed by using the microcytotoxicity test.[4] Twenty-five of the 48 patients were serologically typed for six HLA-DR antigens.[4] Data were expressed as phenotypic frequency in normal whites as compared to herpes stromal keratitis patients typed in

the same laboratory. The frequency of HLA-A, -B, and -C antigens was compared to 545 normal white controls and the HLA-DR antigens compared with 697 normal whites. All HLA typing was performed in the Tissue Typing Laboratory, Department of Surgery, University of California, Los Angeles. The chi-square test with Yates continuity correction for the number of comparisons was used for statistical analysis of the results. The P values were computed by using the Fisher's exact probabilities from the distribution of the chi square. The relative risk, how many times more frequent a disease is in individuals carrying the antigens compared to individuals lacking the antigen, was determined for all antigens.

Results

The HLA-A phenotypes for the 46 patients with herpes stromal keratitis are shown in Table 1. Only the HLA-Aw30 antigen had a P value of less than .05. The relative risk was calculated as 3. However, when the P value for the HLA-Aw30 was corrected[5,6] for the number of variables studied (probability of .03 × 14 antigens typed at the A locus), the corrected P value was .42 and was not significant. No significant associations were noted with HLA-B antigens and herpes stromal keratitis although HLA-B8 was increased (Table 2). There was no increased frequency of HLA-B5 and its split alleles, HLA-Bw51 and HLA-Bw52, in patients with herpes stromal keratitis (Table 2). No significant correlation with the HLA-C antigens was detected (Table 3). Most of the cells typed had none of the 5 HLA-C antigens when tested with antisera identifying these antigens. HLA-DRw3 was detected in 12 of 25 patients (48%) with herpes stromal keratitis as compared to 188 of 697 white controls (27%) with a significant P value of .03 and significant relative risk of 2.5 (Table 4). After correcting the P value for the number of variables studied, the corrected P value was .18, which was not significant.

Discussion

The greatest source of error in attributing an association between HLA and dis-

TABLE 1

HLA-A ANTIGENS AND RECURRENT HERPES STROMAL KERATITIS

HLA Antigens	Normal Whites (N = 545) % Frequency	Herpes (N = 48) % Frequency	Chi Square	P Value*	Relative Risk
A1	28	27	0.01	.9	1.0
A2	51	46	0.22	.6	0.8
A3	20	23	0.05	.8	1.2
A11	12	10	0.01	.9	0.9
A25	4	2	0.03	.9	0.8
A26	7	8	0.02	.9	1.4
A28	8	13	0.79	.4	1.8
A29	7	2	0.94	.3	0.4
Aw23	4	4	0.01	.9	1.3
Aw24	19	15	0.30	.6	0.8
Aw30	6	15	4.76	.03	3.1
Aw31	6	6	0.01	.9	1.2
Aw32	7	10	0.29	.6	1.6
Aw33	1	2	0.11	.7	2.0

*Uncorrected for the number of variables studied.

TABLE 2

HLA-B ANTIGENS AND RECURRENT HERPES STROMAL KERATITIS

HLA Antigens	Normal Whites (N = 545) % Frequency	Herpes (N = 48) % Frequency	Chi Square	P Value*	Relative Risk
B5(Bw51/Bw52)	13	15	.02	.9	0.9
B7	23	17	0.67	.4	0.7
B8	19	29	2.43	.1	1.8
B12(Bw44/Bw45)	27	25	.01	.9	1.1
B13	5	8	0.65	.4	2.1
B14	7	10	0.35	.6	1.7
B15	12	19	1.41	.2	1.8
B17	8	0	3.29	.1	0.1
B18	8	8	0.00	1.0	0.1
B27	7	2	0.87	.4	0.4
B37	3	4	0.16	.7	1.6
B40	12	15	0.05	.8	1.3
Bw22	5	2	0.30	.6	2.4
Bw35	18	15	0.13	.7	0.8
Bw38	6	10	1.13	.3	2.1
Bw39	3	0	0.47	.5	0.4
Bw49	3	4	0.16	.7	1.6
Bw50	3	2	0.04	.8	1.2

*Uncorrected for the number of variables studied.

ease is in the statistical analysis. The number of parameters (HLA specificities) should be accounted for and the final P value should be multiplied by this number to give a corrected P value. An uncorrected P value in our study would have led to a significant association between HLA-Aw30 and HLA-DRw3 and herpes stromal keratitis.

HLA typing of 48 patients with recurrent herpes stromal keratitis failed to support the reported significance of HLA-B5 antigen in recurrent herpes epithelial keratitis. Zimmerman and associates[3] did not correct their P value for number of comparisons made. If they had used this correction method, their results would no longer be significant because their reported P value of .01 becomes a P value of .3 after correction.

The investigation of an HLA disease association has not produced a definite

TABLE 3

HLA-C ANTIGENS AND RECURRENT HERPES STROMAL KERATITIS

HLA Antigens	Normal Whites (N = 545) % Frequency	Herpes (N = 48) % Frequency	Chi Square	P Value*	Relative Risk
Cw1	6	4	0.03	.9	0.8
Cw2	10	8	0.00	1.0	1.0
Cw3	23	25	0.01	.9	1.1
Cw4	16	17	0.02	.9	1.1

*Uncorrected for the number of variables studied.

TABLE 4

HLA-DR ANTIGENS AND RECURRENT HERPES STROMAL KERATITIS

HLA Antigens	Normal Whites (N = 697) % Frequency	Herpes (N= 25) % Frequency	Chi Square	P Value*	Relative Risk
DRw1	17	12	0.1	.7	1.5
DRw2	25	20	0.1	.7	1.4
DRw3	27	48	4.2	.03	2.5
DRw4	15	20	0.2	.7	0.7
DRw5	14	28	3.0	.1	0.4
DRw7	23	36	1.5	.2	0.5

*Uncorrected for the number of variables studied.

answer to the questions of genetic factors in predisposition to herpes stromal keratitis. Further studies are necessary to test the hypothesis and to establish the existence of an association between an HLA antigen and disease severity. In the case of recurrent herpes simplex labialis, the association of HLA antigens and disease remains valid although unconfirmed. Russell and Schlaut's[2] data when corrected for the number of comparisons still show a highly significant association between HLA-A1 and recurrent herpes simplex labialis ($P < .0001 \times 10$ antigens $\pm$ corrected $P < .001$).

Our findings of increased HLA-DRw3 in herpes stromal keratitis prove to be significant on further study. The increase in HLA-B8 is expected and presumably secondary to the increase in HLA-DRw3, reflecting the marked degree of linkage disequilibrium between these two antigens.

SUMMARY

HLA-A, HLA-B, and HLA-C antigens were typed on 48 patients with recurrent herpes stromal keratitis. The HLA-Aw30 antigen occurred three times more frequently in patients with herpes stromal keratitis than in those who lack the Aw30 antigen. When the data for the probability of the HLA-Aw30 were corrected for the number of variables studied, the corrected P value was not significant. A previous report of an increased frequency of HLA-B5 with recurrent herpes keratitis was not confirmed by our study. No significant associations with the HLA-C antigens were noted. HLA-DR antigen typing of 25 herpes stromal keratitis patients indicated that the HLA-DRw3 antigen appeared to have an increased frequency in herpes stromal keratitis. However, the small sample size studied precluded interpretation of the increased phenotypic frequency and the possible association of HLA-DRw3 and herpes stromal keratitis needs further study.

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A SIMPLE HAPLOSCOPIC METHOD FOR QUANTITATING COLOR BRIGHTNESS COMPARISON

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Color brightness comparison is a useful technique for detecting monocular or asymmetric deficits in optic nerve or macular function.[1,2] The test consists of presenting a brightly colored test object alternately to a patient's right and left eyes, and determining whether the eyes perceive the object to be of equal brightness. The test is easily quantitated by using the standard clinical equipment shown in the Figure.

MATERIAL AND METHODS

Two polarizing trial lenses in a standard trial frame are placed in front of each of the patient's eyes. The lens closest to the eye (in the nonrotary lens holder of the trial frame) is oriented so that its axis of polarization is vertical. The lens farthest from the eye (in the rotary lens holder) is oriented with its axis of polarization at some angle A from the horizontal (the angle is simply read from the trial frame). The fraction of light transmitted through the front and rear polarizers is proportional to angle A. (Actually, from the law of Malus,[5] the fraction of the maximal transmission of the front and rear polarizers is $\sin^2 A$). When the front polarizer is at 0 degrees, light transmission is 0; when the front polarizer is at 90 degrees, light transmission is maximal.

The patient looks through the polarizing trial lenses at a uniformly illuminated test slide in a standard viewer for stereoscopic slides. As shown in the Figure, the right eye is presented with the right half of a red, disk-shaped target on a black background. The left eye is presented with the left half of the target.

The test is performed by initially setting angle A for the right eye, A(right eye), to 45 degrees, and angle A for the left eye, A(left eye), to 0 degrees. The patient then looks through the trial frame lenses into the stereoscopic viewer where only the right half of the red disk is seen. The examiner increases A (left eye) (by turning the rotary lens holder in front of the patient's left eye) so that the patient perceives the left half of the red disk. The examiner continues to turn the lens holder until the patient finds that the left half of the target is brighter than its right half, and then back until the left half and the right half of the disk are of equal brightness. The value of A(left eye) for a brightness match, A′, is then simply read from the trial frame, and the percentage difference between the light intensities required by the left eye and the right eye to make the match is read from the Table. If A′ is less than 45 degrees when the left eye is tested in this fashion, less light is required by the left eye to make the match, and the right eye has a deficit in redness perception; if A′ is greater than 45 degrees, more light is required by the left eye, and it is the left eye that has the deficit.

In trials with 25 normal patients, the mean percentage difference in light intensities required by the right and left eyes for a brightness match was 6.5 ± 11 (S.D.). This percentage corresponds to a difference between angles A(right eye) and A(left eye) of less than 2 degrees (5 degrees is the smallest increment marked on

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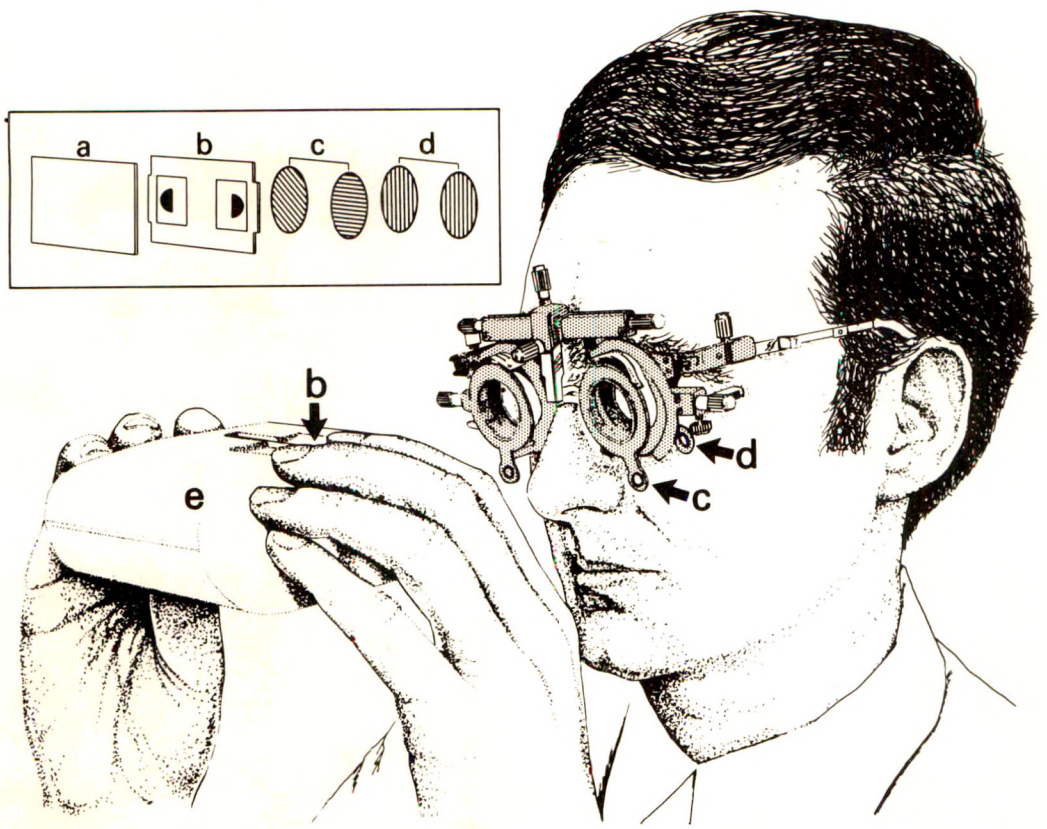

Figure (Mainster and Dieckert). Equipment required for a simple quantitation of the color brightness comparison test: (a) a diffuse illuminated background provided by an ordinary stereoscopic viewer (e); (b) the test slide described in the text that presents the right and left eyes with the right and left halves, respectively, of a red disk-shaped target on a black background; (c) the front polarizers in the rotary lens holders of the trial frame; and (d) the rear polarizers in the fixed lens holders of the trial frame. The axes of the rear polarizers are set at 90 degrees. The test is begun with the axes of the front polarizers of the right and left eyes set at 45 (50% of maximal transmission) and 0 degrees (no transmission), respectively. The front polarizer of the left eye is then gradually turned until a brightness match is achieved as described in the text.

most trial frames). In patients with an advanced visual deficit in the left eye, the lelt half of the target can not be made bright enough to match its right half even with A(left eye) at 90 degrees. In this case, the test is repeated starting with A(left eye) at 45 degrees and increasing A(right eye) from 0 degrees until a brightness match is made as shown previously.

The entire test usually takes less than 30 seconds to perform, and although the luminance produced by most stereoscopes is too low to cause potentially confusing afterimages in a light-adapted patient, the patient is encouraged to make the brightness match as quickly as possible. Any stereoscopic viewer that provides reasonably uniform slide illumination may be used (the adequacy of a particular stereoscope is documented by testing a small number of normal observers). Although polarizing trial lenses are not part of the usual trial lens set, they may be constructed easily from plastic sheet polarizing material (the same material should be used in each of the four

TABLE

COLOR BRIGHTNESS COMPARISON

(A′)*	Fraction of Light Transmitted† (F)	Percentage Difference‡
0	0	100
5	0.008	98
10	0.030	94
15	0.067	87
20	0.117	77
25	0.179	64
30	0.25	50
35	0.329	34
40	0.413	17
45	0.5	0
50	0.587	17
55	0.671	34
60	0.75	50
65	0.821	64
70	0.883	77
75	0.933	87
80	0.970	94
85	0.992	98
90	1	100

*When a brightness match is achieved, A′ is the axis of the front polarizer of the tested eye (the axis of the front polarizer of the opposite eye is always 45 degrees; the axes of both rear polarizers are always 90 degrees).

†Fraction of maximal transmittance (F) of the polarizers in front of the tested eye with the front polarizer at angle A′ and the rear polarizer at 90 degrees. From the law of Malus,[5] $F = \sin^2 A'$. Because the front polarizer in front of the opposite eye is always set at 45 degrees, this fraction is always 0.5 for the opposite eye.

‡Percentage difference between the light intensity needed by the tested eye and that needed by the opposite eye to achieve a brightness match. Because the fraction in the opposite eye is always 0.5, this percentage difference is simply: $\{|F - 0.5| / 0.5\} \cdot 100\%$. When A′ is less than 45 degrees, the tested eye requires less light than the opposite eye (F is less than 0.5); when A′ is greater than 45 degrees, the tested eye requires more light to make the brightness match (F is greater than 0.5).

lenses) or purchased as an inexpensive special order item (from various optical equipment distributors).

Stereoscopic test slides are prepared from two 35-mm color transparencies (of a red half-disk on a black background) mounted appropriately in an ordinary slide mount used for stereoscopic fundus photographs. (The individual color transparencies may be produced by photographing a white half-disk on a black background through a red filter. Kodak Ektachrome 160 [ET 135, tungsten] photographic film was used in this study with 3,200 K [color temperature] tungsten illumination.) The test targets used in this study have a 7-mm radius on the transparency and subtend a 10-degree visual angle in the stereoscope (to encompass the entire perifovea). A red test target has been used because optic nerve defects may produce red perception deficits earlier or disproportionately greater than other measures of macular function such as visual acuity.[1-3] Test slides for different target colors are also readily prepared and may have some value in the identification of other forms of ocular pathology (for example, blue or yellow targets when macular pathology is suspected).[4] It should be noted that color brightness testing is of limited value if different hues are perceived by the patient's right and left eyes. Hue differences have been encountered only rarely in our clinical experience, and most of those have been attributable to marked differences in the status of the preretinal ocular media of the patient's right and left eyes.

With the test slide shown in the Figure, simultaneous visualization of the right and left halves of the red disk target during a brightness comparison results in a comparison essentially of the sensitivities of the nasal halves of the right and left visual fields. Although this simple test does not permit observation of patient fixation and therefore can have little perimetric value, a similar comparison limited largely to the temporal halves of the visual fields may be performed with a test slide that presents the right eye with the left half of the red disk target and the left eye with the right half of the target.

Discussion

The advantages of the above brightness comparison test include the following: (1) it is easily performed and uses equipment already available in the ophthalmic clinic, (2) it provides a consistent end point for testing that varies little with examiner or examination time, (3) it can be used to document the course of an optic nerve or macular problem as well as to screen for the problem, and (4) it could be produced in an inexpensive form (for example, a cardboard box with test slide, plastic polarizers, and disposable flashlight) for home use in following up patients taking drugs that have potential optic nerve or macular toxicity.

Summary

We developed a simple method for quantitating the color brightness comparison test. The testing procedure is quickly performed, uses common ophthalmic equipment, and permits an increased range of applications for the comparison test.

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CONGENITAL ABSENCE OF THE LACRIMAL PUNCTA ASSOCIATED WITH ALACRIMA AND APTYALISM

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Congenital alacrima or absence of tears is a relatively rare disorder of sporadic occurrence and multiple causes including neurogenic abnormalities, a persistent neonatal state, and hypoplasia or absence of the lacrimal gland.[1–3] Mondino and Brown[4] described a family showing autosomal dominant inheritance of congenital alacrima caused by hypoplasia of the lacrimal gland. Congenital alacrima may occur in some patients with anhidrotic ectodermal dysplasia and familial dysautonomia (Riley-Day syndrome). It has also been associated with a lack of salivation.[5] Lacrimal duct defects, particularly absence of puncta and canaliculi, have been long recognized as autosomal dominant traits.[2,3,6–10] A case of lack of salivation and absence of lacrimal puncta has been described.[11] We studied a family in which absence of lacrimal puncta, congenital alacrima, and lack of salivation seemed to be inherited as an autosomal dominant trait. To the best of our knowledge, this combination of abnormalities has not been previously reported.

CASE REPORT

A 9-year-old girl of Italian lineage was examined by one of us (W.C.C.) in August 1978. She complained of blurred vision for distance with variable sandiness and redness of the eyes. The patient had been previously examined at age 13 months because of tearing in both eyes. Examination under general anesthesia disclosed absence of all lacrimal puncta. That true epiphora or even normal tearing did not exist was not recognized at that time. Only subsequent examination years later revealed that the accumulation of mucus material and caking of the eyelid margins had led to a misinterpretation of tearing rather than recognition of a siccant state.

During recent examination the visual acuity without correction was 6/7.5 (20/25) in both eyes and near vision was J 1 at 14 inches in both eyes. The absence of lacrimal puncta was noted. No evidence of dimpling at the potential puncta sites was noted. Bulbar conjunctivae were mildly hyperemic. Corneas were studded with flakes of mucus. Schirmer test without topical anesthesia resulted in no wetting of the test strips. The pupils were equal and reactive. Extraocular muscles were intact. No significant muscle imbalance was noted. Slit-lamp examination revealed not only the previously mentioned flecks of mucus but also a superficial punctate staining of the inferior third of the cornea of each eye after topical application of fluorescein. Tactile tension was grossly normal in both eyes. Applanation tonometry was not done because of the possibility of corneal problems. Cycloplegic refraction revealed a normal hyperopia (+1.00 diopters) in both eyes. Under full mydriasis, direct and indirect ophthalmoscopic examination did not disclose any abnormality of the fundi.

We discussed the congenital alacrima and absence of the lacrimal puncta with the patient's mother who then indicated that the child was under treatment because of an unusual oral problem. There had been early loss of deciduous teeth because of florid caries and the permanent teeth were similarly threatened with rapid destruction by caries. Examination had revealed xerostomia caused by nonfunctioning or absent salivary glands, which was treated with an experimental mouthwash containing calcium and phosphate salts. The mouthwash had also been used in treatment of cancer patients with xerostomia caused by radiation induced destruction of the salivary glands. The patient's mother also mentioned that emotional stresses did not produce tearing of the eyes, that the patient was unable to dissolve hard candy in her mouth, and that her subjective and objective ocular symptoms were increased on windy days and in dry environments.

Similarly affected family members included the patient's 36-year-old father and 64-year-old paternal grandfather (Figure). Examination of the patient's father revealed absence of puncta in the right eye, absence of superior punctum in the left eye, and presence of inferior punctum in the left eye. Schirmer test showed a deficiency in tearing, that is, 10 mm wetting in the right eye and 4 mm wetting in the left eye, which was definitely abnormal for a 36-year-old man. Slit-lamp examination showed no abnormalities. There were flecks of mucus but no staining with fluorescein. Both eyes were free of discomfort except for a subjective tearing sensation in the right eye. There was no history of xerostomia

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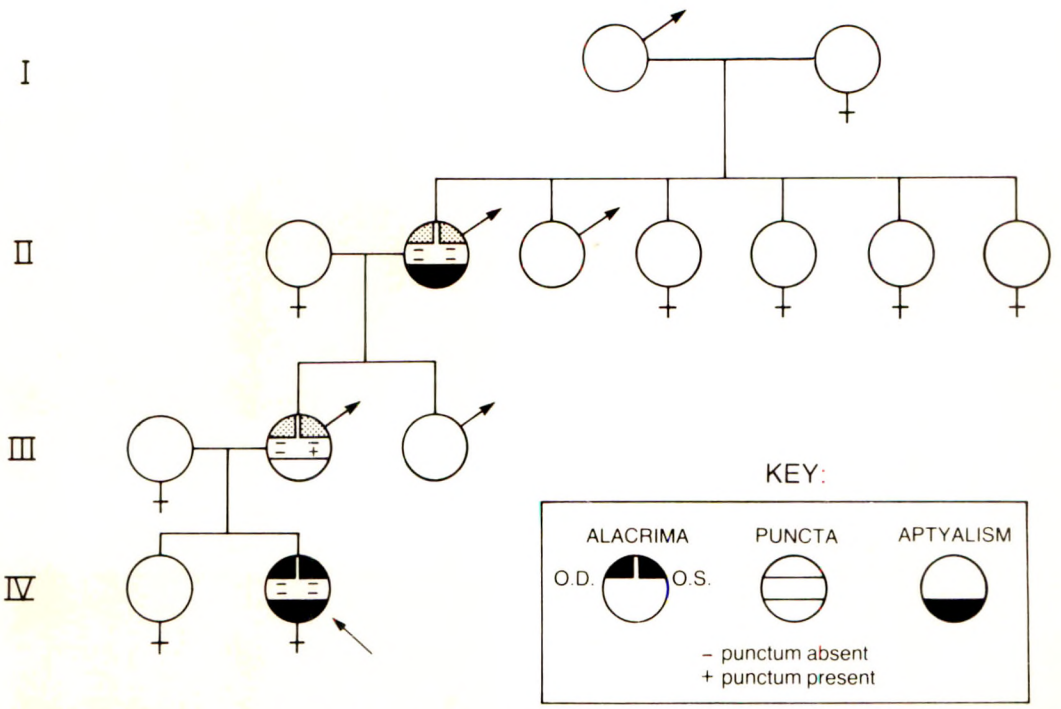

Figure (Caccamise and Townes). Pedigree of family showing autosomal dominant inheritance of alacrima or deficient tearing, absent lacrimal puncta, and aptyalism. Deficient tearing (rather than alacrima) is indicated by shading. Arrow indicates proband (IV-2).

or unusual dental problems. The father's only sibling (a brother) had normal eyes.

All lacrimal puncta were absent in the patient's grandfather. Schirmer test showed a deficiency in tearing, that is, 5 mm wetting in the right eye and 10 mm wetting in the left eye, which was not a normal finding in a 64-year-old man. Results of slit-lamp examination of the corneas were normal. There was no staining with fluorescein. The mouth and tongue were dry. He gave a history of severe dental problems during childhood. Despite frequent dental visits, all teeth were lost because of caries by age 16 years.

Discussion

Congenital alacrima is a relatively rare disorder of varied causes. Sjögren and Eriksen[1] concluded that congenital alacrima could result from neurologic abnormalities in the lacrimation reflex, or a persistent neonatal state, or an aplasia or hypoplasia of the lacrimal gland. In the nine case reports reviewed, no clear instances of a genetic cause were evident. Mondino and Brown[4] reported a family showing autosomal dominant inheritance of congenital alacrima resulting from hypoplasia of the lacrimal gland with no other abnormalities of the adnexa.

In an extensive review of the lacrimation reflex, Mutch[5] described a 67-year-old woman with congenital absence of weeping associated with absence of salivation. She had a lifelong history of never having wept, a dry mouth, and an inability to eat dry food. Hard candy was not dissolved after two hours in the oral cavity, and chewing paraffin for two hours produced minimal amounts of secretion in which there was no ptyalin present. Eyelids were normal and puncta were present and patent.

Blackmar[11] described an 11-year-old boy with a lifelong history of dry mouth with discolored and extensively carious teeth. Ocular cilia were matted together

by mucoid secretion. On crying, there was, however, copious lacrimal secretion. Vision was normal but all lacrimal puncta were absent. Electric shock of the parotid glands produced no visible secretion and inspection and exploration failed to reveal any ductal ostia.

Congenital absence of the lacrimal puncta and canaliculi without other ocular or oral abnormalities has been reported in several families. Sorsby[6] described it in a boy, his father, and probably in the paternal grandmother. Town[7] described a father and his two sons and Bischler[8] described 11 affected individuals in four generations. François[9] described a family with five affected individuals in three generations, and Lumbroso[10] described a family with six affected individuals in three generations. In all of these families, absence of the lacrimal puncta and canaliculi appears to be an autosomal dominant trait with variable expressivity. A comparison of these disorders is shown in the Table.

The trait reported here is readily distinguished from other syndromes in which xerophthalmia and xerostomia may occur. Xerophthalmia and xerostomia occur in Sjögren's syndrome, but this is not a hereditary disorder and occurs primarily in postmenopausal women. Anhidrotic ectodermal dysplasia, an X-chromosome-linked recessive trait, occurs exclusively in males and has features (hypodontia, anodontia, sparse hair, hypoplasia of the sweat glands) that were not present in the family we studied. Familial dysautonomia (Riley-Day syndrome) is a rare autosomal recessive disorder that occurs primarily in Ashkenazi Jews and is characterized by diffuse autonomic dysfunction, mental deficiency, and seizures, which are not present in our patients.

Congenital alacrima caused by hypoplasia of the lacrimal gland has recently been reported to be an autosomal trait in one family,[4] and congenital absence of the lacrimal puncta has been reported to be an autosomal dominant trait in several families. There has been one case report of xerostomia associated with absence of the lacrimal puncta[11] and one case report of alacrima with aptyalism,[5] but no previous reports of a family showing autosomal dominant inheritance of all three defects, that is, congenital alacrima, absence of lacrimal puncta, and lack of salivation as in our case. Autosomal dominant traits frequently show variable expressivity, as we observed (Figure) in our case. The proband shows all features of the trait; the grandfather shows all the features except for the alacrima, which is expressed as a deficiency in tearing. The proband's father shows relatively mild expression with lack of xerostomia, presence of a single punctum, and deficient tearing rather than alacrima. The absence of puncta provides a natural means of minimizing the effects of alacrima. Indeed, surgical obliteration of the puncta

TABLE

ALACRIMA, ABSENT PUNCTA AND APTYALISM

Trait	Alacrima	Absent Puncta	Aptyalism	Inheritance
Absent puncta[1-3,7-10]	No	Yes	No	Autosomal dominant
Hereditary congenital alacrima[4]	Yes	No	No	Autosomal dominant
Alacrima and absent puncta[5]	Yes	Yes	No	None
Absent puncta and salivary glands[11]	No	Yes	Yes	None
Present study	Yes	Yes	Yes	Autosomal dominant

has been used as a form of treatment of congenital alacrima.

Summary

A 9-year-old girl had no lacrimal puncta, tearing (alacrima), or salivation (aptyalism). The lack of salivation caused florid dental caries. The same condition was found in the proband's father and paternal grandfather. Inheritance of this previously unreported trait appears to be autosomal dominant with variable expressivity.

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TRANTAS DOTS AND LIMBAL INFLAMMATION ASSOCIATED WITH SOFT CONTACT LENS WEAR

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Giant papillary conjunctivitis is a well-recognized entity associated with soft and hard contact lens wear.[1] Recent evidence suggests a clinical and histologic similarity, as well as a common immunopathology for the tarsal conjunctival changes found in giant papillary conjunctivitis and vernal conjunctivitis.[2] The limbal form of vernal disease manifests as mucoid, gelatinous nodules and small white superficial spots known as Trantas dots. We encountered a case of vernal-like limbal inflammation and Trantas dots associated with soft contact lens wear.

CASE REPORT

A 30-year-old man had a six-month history of increasing soft contact lens intolerance. Both eyes were red, and the patient complained of severe ocular itching. He had a mucinous discharge, which tended to adhere to the surface of his contact lenses and was difficult to remove. He had been wearing his present set of lenses for ten months. The symptoms became increasingly more severe after he discontinued using his contact lens cleaner three weeks before our initial examination. The patient denied any personal or family history of allergy, atopy, or vernal disease.

Ophthalmologic examination revealed a best corrected visual acuity of 6/6 (20/20) in both eyes. On slit-lamp biomicroscopy we noted a minimal papillary response with no cobblestones or giant papillae of the superior tarsal conjunctivae. The inferior fornix and tarsal conjunctivae were slightly edematous and infiltrated. The bulbar conjunctivae were hyperemic, most marked in the perilimbal area. The conjunctivae at the corneoscleral limbus assumed a diffuse, irregular, raised, mucoid appearance. Numerous discrete white dots were sporadically arranged over the surface of the entire corneoscleral limbus. No corneal, anterior chamber, or lenticular abnormalities were present. Ophthalmoscopic examination was unremarkable.

Scrapings of the corneoscleral limbus and inferior fornix were taken for cytologic examination. Giemsa stain revealed epithelial and mononuclear cells and eosinophils in the limbal and inferior fornix smears. Additionally, polymorphonuclear leukocytes were noted in the smear from the inferior fornix.

The patient was instructed to discontinue contact lens wear. He returned for a follow-up examination two days later and was asymptomatic, with partial resolution of the limbal inflammation and almost total disappearance of the white dots. With the patient's consent a two-day trial of contact lens wear was implemented in an attempt to reproduce the limbal signs. The patient returned with reappearance of the same limbal inflammation and the Trantas dots (Figs. 1 and 2).

DISCUSSION

In 1977 Allansmith and associates[1] described a syndrome of diminished contact lens tolerance and giant papillae in the tarsal conjunctiva of the upper eyelid. It is characterized by erythema of the conjunctiva, excessive mucus production, and ocular itching. These giant papillae clinically resemble the cobblestone papillae found in vernal conjunctivitis. They also share a similar histopathology with infiltrates of mast cells in the epithelium, eosinophils in the epithelium and substantia propria, and basophils in the epithelium and substantia propria.[2–4]

The nature of the cellular infiltrate suggests an immunologic basis for these diseases. Cutaneous basophil hypersensitivity is a form of cell mediated hypersensitivity characterized by the dermal infiltration of basophils and a smaller number of eosinophils.[5] Recent studies have shown that the cellular response in cutaneous basophil hypersensitivity is tissue specific. The reaction is a predominant eosinophilic and a lesser basophilic response when elicited in the guinea pig uvea[6] and conjunctiva.[7] The cutaneous basophil hypersensitivity reaction in the guinea pig conjunctiva has been proposed as an animal model for vernal conjunc-

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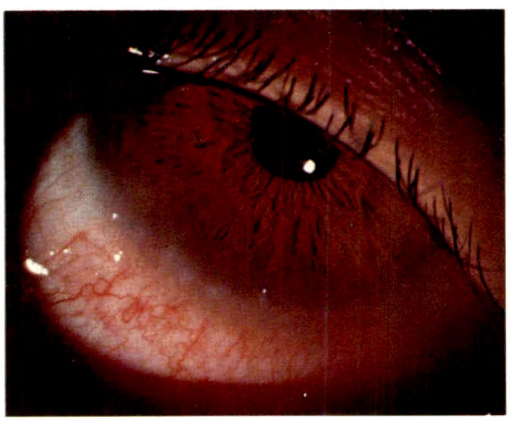

Fig. 1 (Meisler, Zaret, and Stock). Diffuse, irregular, mucoid appearance of the limbal conjunctiva 24 hours after reimplementing contact lens wear.

Fig. 2 (Meisler, Zaret, and Stock). Trantas dots on the raised opaque limbal tissue.

Fig. 3 (Meisler, Zaret, and Stock). Trantas dots at the inferior corneoscleral limbus.

tivitis[7] and cutaneous basophil hypersensitivity has been suggested to be at least in part responsible for vernal disease as well as giant papillary conjunctivitis.[1,2,8]

Contact lens deposits have been implicated as the inciting agent producing vernal-like cobblestones in giant papillary conjunctivitis and it is not unreasonable to expect the same agent to induce vernal-like limbal changes in contact lens wearers. Trantas dots and limbal inflammation are the signs of the limbal form of vernal conjunctivitis. The limbal inflammation initially appears as a hyperemic, edematous, thickened conjunctiva. As the disease progresses the thickening becomes irregular and assumes the appearance of elevated mucoid nodules. Trantas dots are discrete white dots that appear on the apices of these limbal vegetations. They are focal collections of inflammatory cells and degenerating epithelium.[9] Eosinophils are also noted in the dots.[10] The Trantas dots, diffuse limbitis, and limbal nodules present in our patient are compatible with a vernal-like disease, and the scrapings support this diagnosis.

It is doubtful that our patient represents true vernal disease for the following reasons: (1) The limbitis in our patient involved the entire corneoscleral limbus, whereas in vernal disease the changes are usually localized to the superior corneoscleral limbus[9] (Fig. 3). (2) The patient has no family history of atopy or vernal disease.[11,12] (3) He is older than most patients with vernal diseases.[13] (4) Resolution and exacerbation of the condition could be achieved by removing and reintroducing the contact lens, which supports the contention that limbal changes are associated with soft contact lens wear.

Summary

A 30-year-old man developed vernal-like limbal changes associated with soft contact lens wear including Trantas dots, limbal nodules, and diffuse limbitis. These findings add to the contention that the conjunctival changes found in giant papillary conjunctivitis and vernal conjunctivitis share a common immunopathogenesis.

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ASSOCIATION OF HLA-DRw2 ANTIGEN WITH PRESUMED OCULAR HISTOPLASMOSIS

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Presumed ocular histoplasmosis is a clinical entity, which is characterized by a triad of disciform macular scarring, peripapillary scarring, and peripheral atrophic spots. A cause for the dimorphic fungus *Histoplasma capsulatum* is based on clinical[1] and epidemiologic evidence,[2–5] because the organism has not been identified histopathologically in eyes of patients with presumed ocular histoplasmosis syndrome.[6,7] Responses of lymphocytes from patients with clinical ocular disease to yeast phase antigens further support the association of the fungus with the clinical appearance.[8]

Patients with disciform scars of the presumed ocular histoplasmosis syndrome have shown a high frequency of HLA-B7,[9,10] whereas there was no significant increase in the frequency of this antigen in patients with only peripheral atrophic scars without disciform disease.[11] These data imply that there is some genetic component in the pathogenesis of the presumed ocular histoplasmosis syndrome disciform scarring but not necessarily in the development of peripheral atrophic scars.[11,12]

Investigators of HLA and disease associations have frequently recognized that when a disease is associated with a particular allele at the B locus, there may even be a stronger association with an allele at the DR locus.[12] For this reason, we performed DR typing in patients with disciform scarring of the presumed ocular histoplasmosis syndrome and in patients with only peripheral scars of the presumed ocular histoplasmosis syndrome. For comparison, we also studied the incidence of HLA antigens in patients with disciform scarring of degenerative choroidopathy.

SUBJECTS AND METHODS

Twenty-six patients with disciform scarring indicating previous hemorrhagic changes of the presumed ocular histoplasmosis syndrome or with active hemorrhagic lesions in the posterior pole, and at least one of the other two typical types of scars of the triad, were typed for HLA markers.

A population of patients with only peripheral scarring associated with positive skin tests to histoplasmin was selected for HLA typing on the basis of extensive

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epidemiologic studies and characterization of a number of clinical and laboratory factors.[2-5] This group originally consisted of 21 patients identified in a community survey of 842 persons in Walkersville, Maryland. Two had died and one had developed an active peripapillary hemorrhagic lesion at the time when the present study began. Five patients had moved from the Walkersville area but two contributed blood samples at other centers that were sent to Milwaukee for analysis. Thirteen patients still lived in Walkersville and 11 of these consented to HLA typing. Therefore, 13 of the living 18 patients with only peripheral scars from the initial study could be typed for DR antigens.

Eighteen patients with disciform degeneration morphologically the same as the presumed ocular histoplasmosis syndrome disciform scars but thought to have a different etiologic basis were also typed for HLA markers.

Lymphocytes were obtained from preservative-free heparin anticoagulated peripheral blood and isolated by Ficoll-hypaque (density 1.078) differential centrifugation. HLA-A, B, C typing was performed with the standard National Institutes of Health microlymphocytotoxicity technique using 144 HLA typing sera that detected 18 HLA-A, 25 HLA-B, four HLA-C specificities and Bw4/Bw6. B-cell serologic typing for DRw1 to DRw7 was performed by prolonged incubation lymphocytotoxicity testing (one hour with antiserum, two hours with rabbit complement at room temperature) of enriched B lymphocyte preparations made from peripheral blood lymphocytes of carbonyl iron treatment followed by T cell rosette separation with neuraminidase-treated sheep erythrocytes.

Significance levels of differences in antigen frequencies between groups were determined with the chi-square test using Yates correction for discontinuity. The strength of the HLA antigen association was assessed as the relative risk for disease calculated according to Woolf[13] using the following formula:

$$\text{relative risk} = \frac{a \times d}{b \times c}$$

whereby *a* represents the number of patients typing for a certain HLA antigen, *b* the number of patients without that antigen, and *c* and *d* represent the number of normal blood donors with and without the HLA antigen, respectively.

Results

The HLA typing results on 26 patients with presumed ocular histoplasmosis syndrome with disciform macular lesions are shown in Table 1. Twenty patients typed for B7 and 21 patients typed for DRw2; three patients were negative for B7 but positive for DRw2 and two patients were B7 positive but DRw2 negative. Only three out of 26 patients (or 12%) were negative for either antigen.

Table 2 lists the HLA antigen frequencies in the presumed ocular histoplasmosis syndrome patients with disciform scarring, in patients with disciform scarring of degenerative choroidopathy and in normal blood donors. The frequencies of B7 and DRw2 were significantly increased in the presumed ocular histoplasmosis syndrome patients; B7 was present in 20 (77%) ($\chi^2 = 32.7$; $P < 10^{-7}$) and DRw2 was present in 21 (81%) ($\chi^2 = 18.2$; $P < 10^{-5}$) of the presumed ocular histoplasmosis syndrome patients. The relative risks for B7 and DRw2 were 9.5 and 11.7, respectively. In contrast, the frequency of A3 was not significantly increased in this group of patients with the presumed ocular histoplasmosis syndrome ($\chi^2 = 0.07$; $P < .10$) indicating that the A3-B7-DRw2 haplotype common to certain white populations was not associ-

TABLE 1

HLA TYPES OF PATIENTS WITH PRESUMED OCULAR HISTOPLASMOSIS WITH DISCIFORM MACULAR SCARRING

Patient No.	HLA				
	A	B	w4, w6	C	DRw
1	1, 3	7, —	4, 6	—, —	2, —
2	3, —	7, 44	4, 6	—, —	2, 7
3	1, 3	7, 8	6	—, —	2, 3
4	3, —	7, 35	6	4, —	2, 3
5	2, 28	7, 27	4, 6	—, —	2, 4
6	2, 32	7, 15	4, 6	—, —	2, 7
7	11, 32	7, 14	6	—, —	1, 2
8	2, 26	7, 8	6	—, —	1, 2
9	2, 24	7, 27	4, 6	1, —	1, 2
10	1, 2	7, 8	6	—, —	2, 3
11	1, 2	7, 8	6	—, —	2, 3
12	2, 3	7, 22	6	—, —	2, —
13	1, 3	7, 8	6	—, —	2, 3
14	2, 11	7, 50	6	—, —	2, 7
15	1, 2	7, 17	4, 6	—, —	2, 7
16	2, 31	7, 39	6	—, —	2, —
17	3, —	7, 35	6	4, —	1, 2
18	3, 23	7, 49	4, 6	—, —	1, 2
19	2, 32	14, 45	6	—, —	1, 2
20	24, 26	5, 38	4	—, —	1, 2
21	23, 24	8, 22	6	1, —	2, 3
22	2, 11	7, 35	6	4, —	4, 7
23	1, 11	7, 37	4, 6	—, —	6, —
24	1, —	8, 14	6	—, —	3, —
25	26, 28	8, 39	6	—, —	3, 6
26	25, —	15, 44	4, 6	1, 3	4, 7

ated with disciform scarring of the presumed ocular histoplasmosis syndrome. Decreases of the frequencies of other HLA antigens were probably secondary to the increased frequencies of B7 and DRw2. Several HLA antigens (A29, Aw30, B13, B18, B40, Cw2, DRw5) could not be detected in this group of presumed ocular histoplasmosis syndrome patients; however, the relatively small number of patients did not permit any interpretation of these findings. No significant differences in the HLA antigen frequencies could be detected for patients with degenerative choroidopathy when compared with normal blood donors (Table 2).

In Table 3 are shown the HLA types of 13 presumed ocular histoplasmosis syndrome patients with peripheral atrophic scarring. Five (38%) patients typed for B7 and eight (62%) patients typed for DRw2. The DRw2 frequency in the Walkersville group of patients was significantly higher ($\chi^2 = 4.6$; $P = .014$) than that in normal blood donors in Milwaukee. In contrast to the absence of B18, B40, and Cw2 in the presumed ocular histoplasmosis syndrome patients with disciform scarring it was possible to detect these antigens in this group of patients of the presumed ocular histoplasmosis syndrome patients

TABLE 2

HLA ANTIGEN FREQUENCIES IN PATIENTS WITH DISCIFORM SCARRING OF PRESUMED OCULAR HISTOPLASMOSIS AND DEGENERATIVE CHOROIDOPATHY

HLA-A	Presumed Ocular Histoplasmosis (N = 26) %	Degenerative Choroidopathy (N = 18) %	Normal Blood Donors (N = 3,240) %
A1	31	33	29.5
A2	46	61	51.1
A3	31	17	26.5
A11	15	0	10.9
Aw3	8	0	3.7
Aw24	12	28	17.5
A25	4	11	5.3
A26	12	6	6.9
A28	8	6	6.9
A29	0	0	5.6
Aw30	0	11	4.4
Aw31	4	11	3.9
Aw32	12	6	6.8
Aw33	0	0	1.4
B5	4	17	11.7
B7	77	17	25.6
B8	31	22	21.3
B13	0	11	6.6
B14	12	0	5.9
B15	8	28	12.8
B17	4	17	8.7
B18	0	22	9.9
Bw22	8	0	4.1
B27	8	0	9.1
Bw35	12	6	17.2
B37	4	0	1.9
Bw38	4	0	4.0
Bw39	8	0	4.2
B40	0	22	14.1
Bw44	8	27	25.0
Bw45	4	0	0.9
Bw49	4	0	3.2
Bw50	4	0	1.5
Bw4	38	44	63.0
Bw6	96	78	87.0
Cw1	12	11	6.6
Cw2	0	6	14.2
Cw3	4	22	18.4
Cw4	12	11	19.1
DRw1	27	6	12.0*
DRw2	81	22	28.0
DRw3	31	11	27.0
DRw4	12	44	32.0
DRw5	0	22	22.0
DRw6	8	22	22.0
DRw7	23	22	30.0

*60 normal blood donors were typed for DRw.

TABLE 3

HLA TYPES OF PATIENTS WITH PRESUMED OCULAR HISTOPLASMOSIS WITH PERIPHERAL LESIONS (WALKERSVILLE, MARYLAND)

Patient No.	HLA				
	A	B	w4, w6	C	DRw
1	24, —	7, —	6	3, —	2, —
2	1, 2	7, —	6	—, —	2,
3	3, —	7, —	6	—, —	2, —
4	1, 2	7, —	6	—, —	1, 2
5	1, 2	7, 40	6	—, —	2, (3)
6	11, 26	5, 35	4, 6	—, —	2, 5
7	1, 26	5, 8	4, 6	—, —	2, 3
8	25, 31	5, 18	4, 6	—, —	2, —
9	2, 24	8, 44	4, 6	—, —	4, —
10	1, 26	8, 35	6	4, —	3, 6
11	3, 23	35, 49	4, 6	—, —	1, 6
12	1, 3	8, 18	6	—, —	4, —
13	1, 32	8, 40	6	2, —	3, 4

with peripheral atrophic lesions. These data seem to indicate that no HLA antigen had a particularly low frequency in the presumed ocular histoplasmosis syndrome patients.

DISCUSSION

The present data suggest that DRw2 is strongly associated with the presumed ocular histoplasmosis syndrome, not only at the stage of disciform scarring, but also at the stage when peripheral atrophic lesions occur. We also observed a considerable increase of the frequency of B7 in the presumed ocular histoplasmosis syndrome patients with disciform scarring similar to previous observations by Braley and associates,[10] and Godfrey, Sabates, and Cross.[9] Conversely, this study and a previous observation[11] did not show a significant increase of the frequency of B7 in the presumed ocular histoplasmosis syndrome patients with peripheral atrophic spots, suggesting that the B7 association with the presumed ocular histoplasmosis syndrome was restricted to the stage of disciform scarring.[11] The present findings of an increased frequency of DRw2 (62%) in the Walkersville, Maryland, patients with peripheral lesions indicate that an HLA association may play a role in the pathogenesis of the early lesions of the eye after *H. capsulatum* infection. However, the small group of the Walkersville patients tested for HLA and our inability to test a normal control population in the same geographic area may restrict the interpretation of our findings.

Disciform lesions secondary to degenerative choroidopathy are similar to those of the presumed ocular histoplasmosis syndrome but are associated with autosomal dominantly inherited drusen[14] and are found in older age groups. Studies of a random population of patients with this disorder did not identify any HLA antigen association, implying the presence of genetic differences in the pathogenesis of the two types of macular disciform scarring despite their morphologic and histopathologic similarities.[15,16]

Exposure to *H. capsulatum* has been documented by skin tests that are positive in 70 to 90% of the population in some parts of the United States but it is rarely associated with significant health problems. Our findings indicate a genetic component in the susceptibility of development of morphologic changes in the eye after infection with *H. capsulatum*. The gene or genes responsible for this susceptibility may be identical to the DRw2 gene or closely associated with it on the sixth chromosome. The function of DR gene products is not understood but it is thought that they are involved in some aspect of the control of immune responses similar to the Ia (immune associated) region genes of the equivalent H-2 system in the mouse. In addition to this implica-

tion of host factors in the production of scarring in the eye, primate studies using arterial injection of the fungus show the importance of inoculum size, phase of the organism, and site of injection in production of the ocular lesions.[17]

Previous studies have suggested that immune hyporesponsiveness may be related to the presence of B7 and DRw2.[18] The presumed ocular histoplasmosis syndrome patients with macular scarring do, however, have an increased reactivity on skin testing to histoplasmin,[19] react to a greater number of skin tests than do other uveitis patients,[20] and show normal lymphocyte stimulation to antigens prepared from yeast phase *H. capsulatum*.[8]

Pathogenetic mechanisms may be shared by diseases that show association with the same HLA antigens. Other abnormal states known to correlate with DRw2 are multiple sclerosis,[21,22] Goodpasture's syndrome,[23] idiopathic optic neuritis,[24] and homogeneous immunoglobulinemia.[25] Although the cause of multiple sclerosis is unknown, it is postulated that after exposure to a ubiquitous agent (perhaps measles), the susceptible individual develops a modified form of disease that runs a relapsing course. This modified form of disease may be immunologically mediated.[22] A similar series of events has been proposed for the presumed ocular histoplasmosis syndrome.[19,26] Early infection with the agent is thought to occur in the teenage years,[5] but the pattern of peripheral spots may change for many years thereafter.[27] Macular disciform scars probably occur ten to 30 years after initial infection,[5] and their form can show continued alternations over many years of follow-up after they are established.[28] Whether the formation of a disciform scar is the result of an immunologically mediated event or hemodynamic decompensation of an atrophic spot is not yet known.[29]

Of interest is the increased frequency of B7 and DRw2 observed in patients with homogeneous immunoglobulinemia that is associated with autoimmune disease, primary immunodeficiency, neoplasia, or prolonged antigen stimulation. This condition may represent defective regulation of antibody synthesis or antigen clearance, or both. Goodpasture's syndrome[30] in the eye interestingly has been associated with layering of IgG in linear deposits along Bruch's membrane and in the basement membrane of choroidal vessels.

Summary

Patients with presumed ocular histoplasmosis syndrome were typed for HLA-A, B, C, and DR antigens. It was found that 21 (81%) of 26 of the presumed ocular histoplasmosis syndrome patients with disciform macular scarring and 8 (62%) of 13 of the presumed ocular histoplasmosis syndrome patients with peripheral atrophic spots typed for DRw2. The frequency of DRw2 in normal blood donors was 28%. The 77% (20 patients) frequency of B7 in 26 of the presumed ocular histoplasmosis syndrome patients with disciform scarring was also significantly higher than the 25.6% frequency of B7 in normal blood donors. In contrast, no significant differences were observed in any HLA antigen frequency for patients with disciform scarring of degenerative choroidopathy. These observations suggest that an association with DRw2 may play a role in the pathogenesis of the eye lesions after *Histoplasma capsulatum* infection.

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MACULAR LESIONS IN BLACKS WITH THE PRESUMED OCULAR HISTOPLASMOSIS SYNDROME

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The occurrence of subretinal neovascularization in blacks with the presumed ocular histoplasmosis syndrome appears to be unusual and previous cases have not been documented by clinical history and angiography in published reports. Schlaegel[1] found that only 0.7% of his patients with the presumed ocular histoplasmosis syndrome were black. Without citing individual cases, he estimated that the frequency of macular involvement in blacks is one-sixth that of whites although the punched out spots and sensitivity to histoplasmin appear to occur with the same frequency in whites and blacks. Recent reports[2,3] indicate an increased frequency of HLA B-7 in patients with presumed ocular histoplasmosis syndrome.

We describe six black patients with presumed ocular histoplasmosis syndrome in whom macular lesions were present, and report the HLA types of four of these six patients.

CASE REPORTS

Case 1—A 30-year-old, Alabama-raised black woman noted blurred vision for two weeks in her left eye. She had been treated for one week with 60 mg of prednisone daily before referral here. A similar episode had occurred in the right eye two years previously and had resolved with the use of systemic corticosteroids. Her best corrected visual acuity was R. E.: 6/6 (20/20) and L. E.: 6/15 (20/50). Results of slit-lamp examination were normal. Intraocular pressures by applanation tonometry were normal. The pupils were equal and reactive in both eyes. No afferent pupillary response was present.

Ophthalmoscopic examination of the right eye (Fig. 1) showed mild peripapillary atrophy, peripheral punched out scars, and an apparent subretinal neovascular membrane in the macula surrounded by pigmented and depigmented halos. A fluorescein angiogram of the right macula (Fig. 2) confirmed the presence of the subretinal neovascularization. Ophthalmoscopic examination of the left eye showed mild peripapillary atrophy and peripheral atrophic lesions. Serous elevation of the macula with localized subretinal hemorrhage and lipid exudates was noted (Fig. 3). A green-gray subretinal membrane was noted. The angiogram (Fig. 4) confirmed the presence of a small subretinal neovascular membrane and blockage of some fluorescence by subretinal hemorrhage. A chest roentgenogram showed a calcified node in the right hilus and a calcified granuloma in the right middle lobe consistent with old pulmonary histoplasmosis. No skin test was performed. HLA typing showed the absence of the HLA B-7 antigen (Table). The patient's prednisone dosage was gradually tapered and her vision remained unchanged. Five months later, she again complained of blurred vision in the left eye. Visual acuity in the left eye had decreased to 6/21 (20/70).

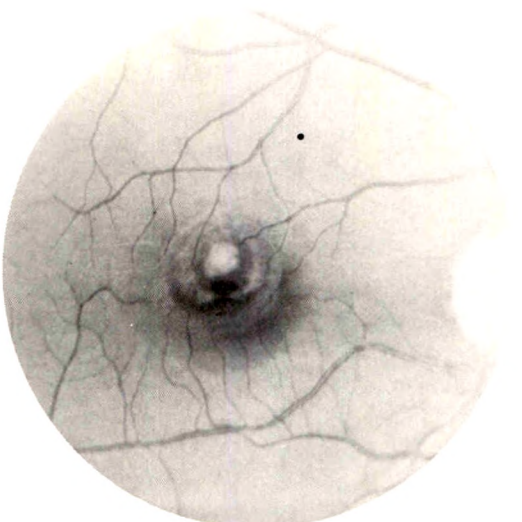

Fig. 1 (Baskin and associates). Case 1. Right eye, Subretinal neovascular membrane with surrounding hyperpigmented and hypopigmented rings is seen. Pigmentary changes are probably secondary to previous local detachments that have settled.

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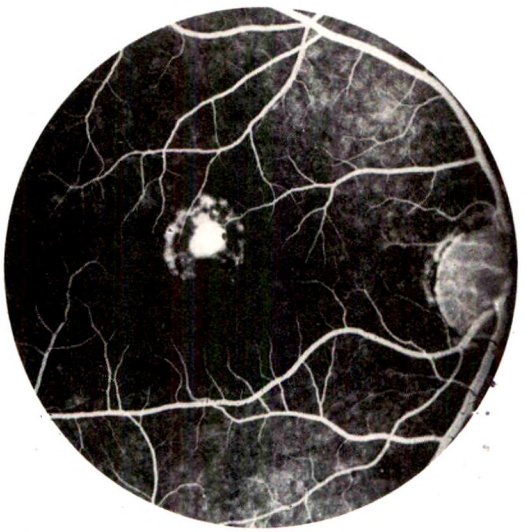

Fig. 2 (Baskin and associates). Case 1. Right eye, Fluorescein angiogram shows central hyperfluorescent area with surrounding lacy pattern of subretinal vessels.

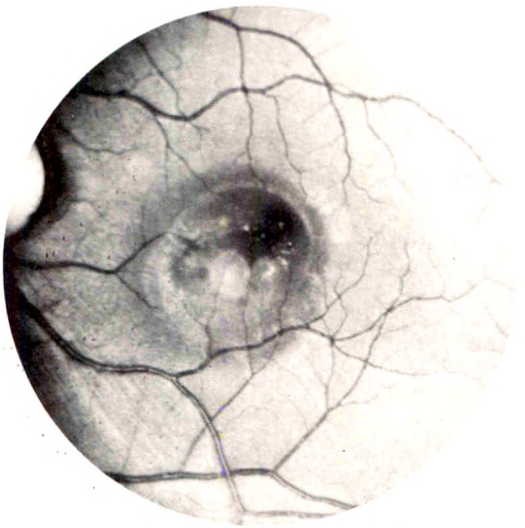

Fig. 3 (Baskin and associates). Case 1. Left eye, Localized serous detachment of macula with some subretinal exudation and hemorrhage.

Ophthalmoscopic examination showed an increase in the amount of serous elevation. A fluorescein angiogram showed that the neovascular net had become larger and that a hyperpigmented halo was present similar to the one seen in the fellow eye (Fig. 5). The right eye was unchanged. Systemic corticosteroids were resumed with subsequent improvement of visual acuity to 6/15 (20/50) one month later.

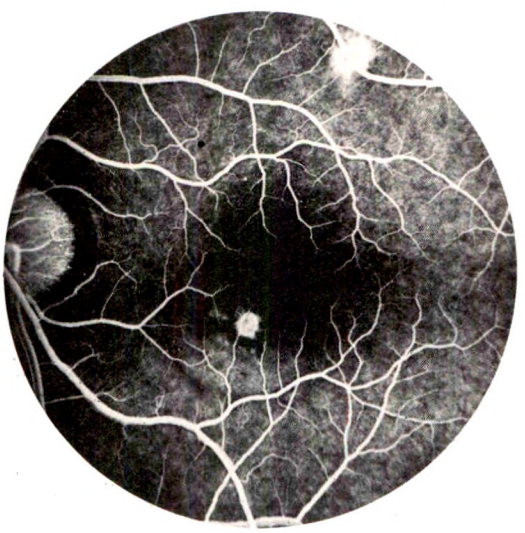

Fig. 4 (Baskin and associates). Case 1. Left eye, Fluorescein angiogram shows small area of subretinal neovascularization under macula and punched-out spots under the superotemporal vessels.

Case 2—A 43-year-old black man reported a two-week history of decreased vision in his right eye. He had lived in Louisiana until age 21 years, and was in contact with farm animals. Since then, he has lived in Chicago. His best corrected visual acuity was R. E.: 6/21 (20/70) and L. E.: 6/6-3 (20/20-3). Results of slit-lamp examination were normal. Intraocular pressures by applanation tonometry were R. E.: 10 mm Hg and L. E.: 14 mm Hg. The pupils were equal and reactive. No afferent pupillary response was present.

Ophthalmoscopic examination of the right eye (Fig. 6) disclosed peripheral atrophic lesions, peripapillary atrophy, and a small subretinal hemorrhage in the macula. There was surrounding serous elevation of the retina, and an atrophic lesion superotemporal to the macula. Fluorescein angiography of the right macula showed an area of hyperfluores-

TABLE

HLA ANTIGEN TYPES IN BLACKS WITH PRESUMED OCULAR HISTOPLASMOSIS SYNDROME

Case No.	Locus A	Locus B
1	2,W36	W17,W35
2	W32,W33	5,W15
5	11, 29	7, 18
6	2,W23	W15,—

Fig. 5 (Baskin and associates). Case 1. Left eye, Taken five months after Figure 4; subretinal neovascularization has increased in size.

Fig. 6 (Baskin and associates). Case 2. Right eye, Peripapillary atrophy and superotemporal punched out spots are seen. Macular area shows some serous elevation of the macula and a small area of subretinal hemorrhage.

cence that increased in size and intensity in the later phases (Fig. 7). This area was interpreted as a subretinal neovascular membrane. Ophthalmoscopic examination of the left eye showed peripheral atrophic scars only. A chest roentgenogram was normal. The histoplasmin skin test developed 18 mm of induration at 24 hours. Complement-fixing antibodies to the yeast-phase antigen of *Histoplasma capsulatum* were present at a 1:8 titer and the mycelial phase at a 1:16 titer. HLA typing showed the absence of the B-7 antigen (Table).

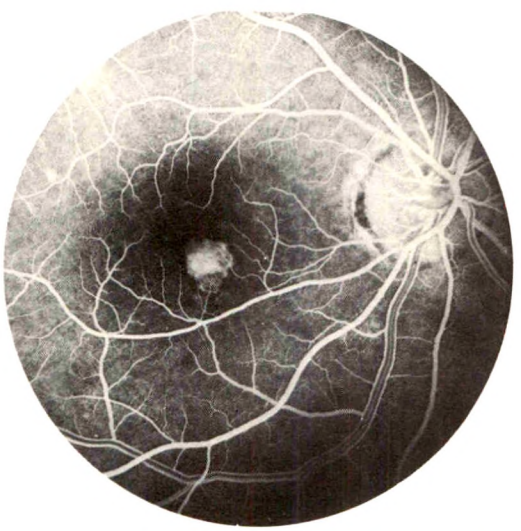

Fig. 7 (Baskin and associates). Case 2. Right eye, Angiogram confirms presence of submacular neovascular membrane, peripapillary pigmentary changes and punched-out spot superotemporal to the macula.

Case 3—A 37-year-old Mississippi-born black man complained of decreasing vision in his right eye at age 25 years. He had previously noted a loss of vision in his left eye at age 19 years. His best corrected visual acuity was R. E.: 6/9+2 (20/30+2) and L. E.: 6/120 (20/400). Results of slit-lamp examination were normal. The intraocular pressure by applanation tonometry was 14 mm Hg in both eyes. The pupils were 3 mm and reactive. No afferent pupillary response was present.

Ophthalmoscopic examination showed peripapillary atrophy and peripheral atrophic lesions in both eyes. An atrophic lesion was present inferior to the macula in the right eye (Fig. 8). Fluorescein angiography of the right eye showed peripapillary hyperfluorescence, slight hyperfluorescence under the fovea, and a well-demarcated hyperfluorescent area inferior to the macula (Fig. 9). Ophthalmoscopically, peripapillary atrophy and a disciform lesion with evidence of the subretinal neovascularization were present in the left eye (Fig. 10). Fluorescein angiography of the left eye confirmed the presence of this neovascular membrane as well as peripapillary hyperfluorescence and multiple well-circumscribed areas of pigment mottling (Fig. 11). A chest x-ray film was normal. A histoplasmin skin test developed 10 mm of induration at 48 hours. Complement-fixing antibodies to the yeast-phase antigen of *H. capsulatum* were present at a 1:8 titer; anti-

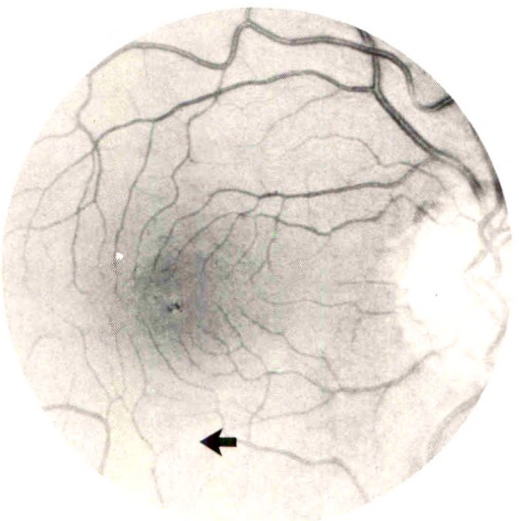

Fig. 8 (Baskin and associates). Case 3. Right eye, Peripapillary atrophy, pigment mottling in fovea, and an atrophic spot inferior to macula (arrow) are seen.

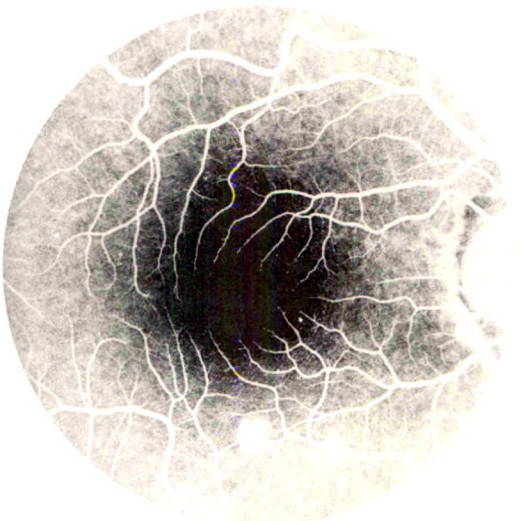

Fig. 9 (Baskin and associates). Case 3. Right eye, Fluorescein angiogram shows window defect inferior to the macula and slight hyperfluorescence directly under fovea.

bodies to the mycelial phase were absent. HLA typing was not performed.

Case 4—A 26-year-old Chicago-born black man described a one-month history of decreasing vision in his left eye. Two months previously, he had been struck in the same eye. His best corrected visual acuity was R. E.: 6/7.5 (20/25) and L. E.: 6/9 (20/30). Results of slit-lamp examination were normal. The pupils were 3 mm and reactive. No afferent pupillary response was present.

Ophthalmoscopic examination revealed peripapillary atrophy in both eyes, a single atrophic peripheral lesion in the right eye, and retinal pigment epithelial changes in the macula of the left eye.

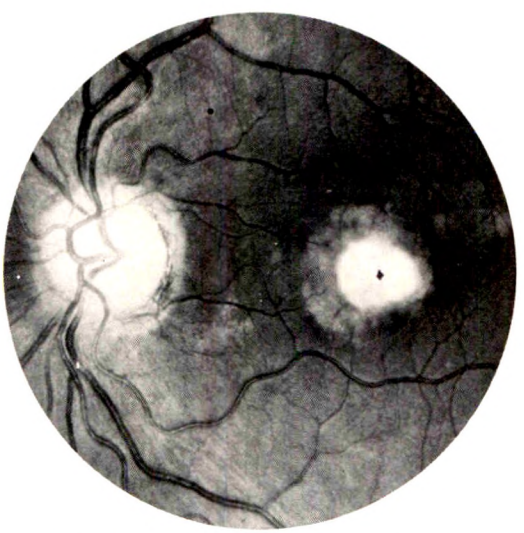

Fig. 10 (Baskin and associates). Case 3. Left eye, Prominent peripapillary atrophy and disciform macular scar with surrounding pigmentary mottling seen.

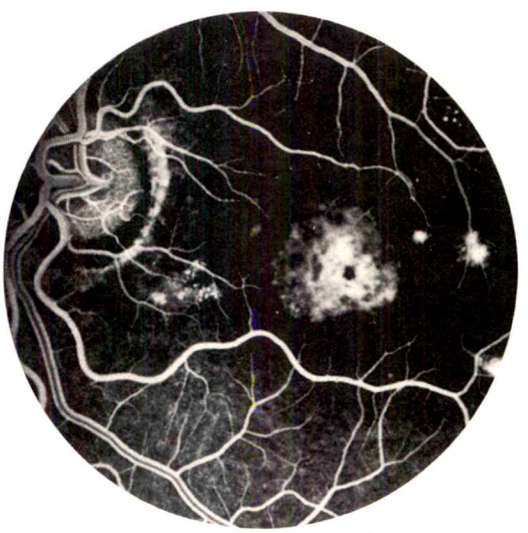

Fig. 11 (Baskin and associates). Case 3. Left eye, Fluorescein angiogram shows submacular neovascularization and surrounding pigment epithelial window defects.

Fluorescein angiography of the left eye showed an area of peripapillary hyperfluorescence and a well-circumscribed area of hyperfluorescence temporal to the macula. A chest x-ray film was normal. The histoplasmin skin test developed 20 mm of induration at 48 hours. Complement-fixing antibodies to both the yeast and mycelial phases of *H. capsulatum* were negative. HLA tissue typing was not performed.

Case 5—A 56-year-old Georgia-born black man described poor vision in both eyes since age 32 years, when he had had hemorrhages in both eyes and was treated by an ophthalmologist with vitamins and other pills. His vision at that time improved slightly and had since remained stable. He lived in Georgia until age 15 years, in Ohio until age 24 years (where he lived on a farm), and in Chicago up to the present time. His best corrected visual acuity was R. E.: 6/120 (20/400) and L. E.: counting fingers. Results of slit-lamp examination were normal. The intraocular pressures by applanation tonometry were R. E.: 17 mm Hg and L. E.: 19 mm Hg. No afferent pupillary response was present.

Ophthalmoscopic examination of the right eye showed prominent peripapillary atrophy and peripheral chorioretinal scars (Fig. 12). The macula contained a large inactive disciform scar with surrounding mottling of the retinal pigment epithelium. Ophthalmoscopic examination of the left eye showed similar changes. The chest roentgenogram was normal. A histoplasmin skin test developed 25 mm of induration at 24 hours. HLA tissue typing showed the presence of B-7 antigen (Table).

Case 6—A 58-year-old Chicago-raised black woman had been aware of poor vision in her left eye for at least one year. As a child she visited a farm in Texas for a few weeks each year. Her best corrected visual acuity was R. E.: 6/7.5 (20/25) and L. E.: 6/60 (20/200). Results of a slit-lamp examination were normal. Intraocular pressure by applanation tonometry was 15 mm Hg in both eyes. No afferent pupillary response was present.

Ophthalmoscopic examination revealed a tilted disk, peripapillary atrophy, and multiple peripheral atrophic lesions in both eyes; a macular hole was seen in the left eye (Fig. 13). The chest x-ray film was normal. There was no reaction at 48 hours to a histoplasmin skin test. HLA tissue typing showed the absence of the B-7 antigen (Table).

Discussion

Subretinal neovascularization and disciform degeneration of the macula appear rarely in blacks. Senile macular degeneration, for example, is seen much less frequently in blacks than in whites.[4] Despite numerous reports of large series of patients with presumed ocular histoplasmosis syndrome, the characteristic disciform lesion in blacks has not been published. Gass and Wilkinson[5] reported a series of 130 patients with presumed ocular histoplasmosis syndrome. There were no blacks in their series. In Schlaegel and associates' report,[6] of 190 patients with histoplasmic choroiditis, none were

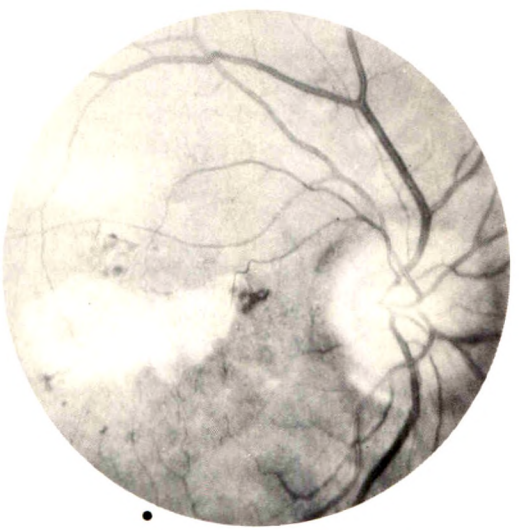

Fig. 12 (Baskin and associates). Case 5. Right eye, Prominent peripapillary atrophy and large inactive disciform macular scar are seen.

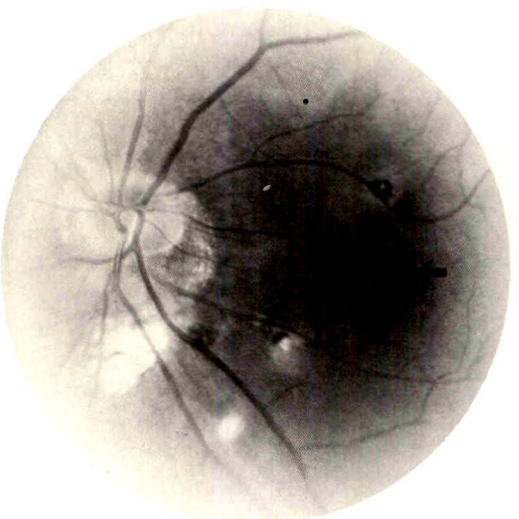

Fig. 13 (Baskin and associates). Case 6. Left eye, Multiple punched-out spots are seen. A small tilted myopic disk is present with prominent peripapillary changes. A macular hole is seen (arrow).

black. Makley and associates[7] described 79 cases and Krill and associates[8] described 45 cases of histoplasmic choroiditis; there was one black patient in each series but the condition of their maculae was not described. Schlaegel[1] has recently estimated that macular involvement in presumed ocular histoplasmosis syndrome is six times more common in whites than in blacks.

In our series, the six black patients with the presumed ocular histoplasmosis syndrome ranged in age from 26 to 58 years. They were all born or raised near the Mississippi River Valley, the endemic area for histoplasmosis. Our criteria for diagnosis included the appearance of at least two of the following signs: (1) serous and hemorrhagic detachment of the macula with subretinal neovascularization; (2) peripapillary chorioretinal atrophy; or (3) peripheral atrophic chorioretinal scars. One patient also showed a macular hole. Four of the five patients who had skin tests had positive responses to histoplasmin. Macular involvement was bilateral in three of the six cases.

Macular involvement in whites with the presumed ocular histoplasmosis syndrome appears to correlate with the presence of HLA B-7.[2,9] Although whites with only peripheral lesions had the same frequency of B-7 as the general population (20%),[3] white patients with macular involvement had the B-7 antigen 55 or 78% of the time.[2,9] HLA typing was performed in four of our black patients with presumed ocular histoplasmosis syndrome. One showed the presence of HLA B-7 (Table). The small numbers involved prevent a comparison with the 55 or 78% frequency of HLA B-7 in white patients with macular involvement in the presumed ocular histoplasmosis syndrome. The one black patient with presumed ocular histoplasmosis syndrome previously HLA typed did not have HLA B-7.[9] In general HLA B-7 antigen appears to be slightly rarer in blacks[10,11] than whites but the discrepancy does not appear to be enough to explain the rarity of macular involvement in blacks with presumed ocular histoplasmosis syndrome.

Clinical assessment of the frequency of diseases in different races may be misleading. An apparent racial difference may be related to genetic or environmental factors. Additionally, a disease may be overlooked or its clinical appearance may differ between races. Many diseases have been reported to occur less frequently in blacks. Presumed ocular histoplasmosis syndrome is one such disease. Although a prevalence cannot be shown from this series, we wish to point out that presumed ocular histoplasmosis syndrome with macular involvement can occur in blacks, and this entity must be considered in the differential diagnosis of a disciform or atrophic macular lesion in a black individual.

Summary

Six black patients had fundus lesions diagnostic of the presumed ocular histoplasmosis syndrome. All patients had peripapillary changes or peripheral punched-out chorioretinal lesions, or both. Five of the six had macular subretinal neovascularization, disciform scarring, or an atrophic macular lesion, and one patient had a macular hole; four of five patients tested had a positive histoplasmin skin test. The macular involvement was bilateral in three of the six cases. HLA B-7 was present in one of four patients who had HLA typing. Macular involvement can occur in blacks with the presumed ocular histoplasmosis syndrome.

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OPHTHALMIC MINIATURE

Of course there is the long-held belief that gemstones ward off sickness, and this was very much in evidence during the Middle Ages. For example, it was thought that garnets were a remedy for a feverish illness. The Zircon was popular in the Fourteenth Century as a safeguard against the Black Death and diamonds were also thought to be a protection against plague.

At this time the opal was known as ophthalmioe, or eye-stone. When wrapped in a bayleaf and worn constantly it was thought to improve the eyesight. The emerald has had a connection with eyes for centuries past. This could be considered as part of the reason why green is supposed to be the most restful color for the eyes. Going back to Roman times, Nero, who had very bad vision, was said to use a slice of emerald to improve his sight while watching the gladiators in the arena.

Joan Frank, *The Beauty of Jewelry*
London, Crescent Books, 1979

OCULAR INFLAMMATION ASSOCIATED WITH *YERSINIA* INFECTION

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Ocular involvement in patients with *Yersinia* infection is uncommon. *Yersinia enterocolitica*[1] and *Y. pseudotuberculosis*[2,3] may cause Parinaud's oculoglandular syndrome, and *Y. enterocolitica* has been isolated from the eye in a few patients.[4,5] Uveitis or conjunctivitis are occasionally associated with *Yersinia* infection.[6–10] However, data regarding detailed ophthalmologic findings concerning endogenous uveitis and conjunctivitis associated with *Yersinia* infection have been lacking. We studied the clinical appearance of uveitis and conjunctivitis associated with *Yersinia* infection in 23 patients.

SUBJECTS AND METHODS

Twenty-three patients, 13 males and ten females, ranging in age between 16 and 47 (mean 28) years were included in this study. The data were collected during the ten-year period between 1969 and 1978. Eleven patients were from Southern Finland, four were from Central Finland, and eight patients were from Northern Finland. In serologic tests, the criterion of recent *Yersinia* infection was a maximum agglutinin titer of at least 160, combined with a significant rise of the titer (at least two twofold dilution steps when tested in parallel) in the acute phase, or followed by a significant drop of the titer within six months, or both. The patients underwent a medical and ophthalmologic examination and follow-up throughout the course of the acute infection. Color photography of the anterior eye was performed in three patients and fluorescein angiography of the iris in one patient (Case 11) during the acute stage of ocular inflammation. Twenty patients underwent x-ray examination of the lumbosacral spine. Determination of HLA-antigens using the two-stage microcytotoxicity method[11] was done in 17 patients.

RESULTS

The disease was characterized by acute onset. Sixteen patients had fever that rose to a maximum between 37.6 and 39.7°C (mean 38.6°C). Acute abdominal symptoms with a duration of up to three weeks occurred in 19 patients; 16 had diarrhea and nonspecific abdominal pain, one patient had only diarrhea, and two only abdominal pain (Table 1). Two patients (Table 1, Cases 5 and 19) had emesis, and one patient (Table 1, Case 8) had anorexia. From one to three weeks after onset of the illness, 22 patients developed arthritis showing acute onset with severe symptoms and lasting usually less than six months. Two patients

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TABLE 1

SURVEY OF THE CLINICAL PATTERN*

Patient No., Age (yrs), Sex	Fever (°C)	Abdominal Symptoms: Diarrhea	Abdominal Symptoms: Pain	Arthritis, Arthralgia	Myalgia	RS	AS, SI	AAU	Conjunctivitis
1, 23, M	38.5	−	−	+	+	+	SI	+	−
2, 37, M	—	+	−	+	+	+	AS	+	−
3, 29, M	37.9	−	+	+	+	−	SI	+	−
4, 29, M	38.2	+	+	+	−	+	—	+	+
5, 23, F	39.4	+	+	+	+	+	—	+	−
6, 30, M	—	−	−	+	+	+	SI	+	−
7, 21, F	—	+	+	+	+	−	SI	+	−
8, 31, F	38.0	+	+	+	+	−	—	+	−
9, 16, M	—	−	+	−	−	−	—	+	+
10, 18, F	38.5	−	−	+	−	+	—	+	+
11, 46, F	—	+	+	+	−	−	SI	+	−
12, 47, F	—	+	+	+	−	−	—	+	—
13, 24, M	38.6	+	+	+	−	−	SI	+	−
14, 28, F	—	−	−	+	+	−	SI	+	−
15, 41, F	39.0	+	+	+	+	−	SI	+	−
16, 31, M	39.0	+	+	+	−	−	—	+	−
17, 21, M	38.8	+	+	+	−	+	SI	+	−
18, 41, F	38.3	+	+	+	−	−	SI	−	+
19, 22, M	39.0	+	+	+	+	+	SI	−	+
20, 16, M	38.7	+	+	+	−	+	—	−	+
21, 34, F	38.5	+	+	+	−	+	—	−	+
22, 29, M	37.6	+	+	+	+	−	—	−	+
23, 17, M	39.7	+	+	+	−	+	—	−	+

*RS designates Reiter's syndrome; AS, ankylosing spondylitis; SI, sacroiliitis, AAU, acute anterior uveitis + designates symptom was present; −, that symptom was absent.

(Cases 18 and 19) had had reactive polyarthritis 24 and six years before *Yersinia* arthritis. Eleven patients had myalgia and arthritis. One patient (Case 14) developed carditis during the acute stage of *Yersinia* infection. Eleven patients developed Reiter's syndrome with arthritis, dysuria or pyuria, and ocular inflammation. Seventeen patients (Table 1, Cases 1-17) had acute anterior uveitis, and nine (Table 1, Cases 4, 9, 10, and 18-23) had conjunctivitis associated with the acute stage of *Yersinia* infection. One patient with acute anterior uveitis (Case 12) had had unilateral acute anterior uveitis three years and another (Case 13) ten months earlier. One patient with acute anterior uveitis (Case 17) had had unilateral acute anterior uveitis twice three and four years earlier, respectively. One patient with conjunctivitis (Case 18) had suffered from unilateral, recurrent acute anterior uveitis 15 years earlier.

Symptoms of sacroiliitis were present in 12 patients. One of these patients (Table 1, Case 2) had had ankylosing spondylitis for 13 years before onset of *Yersinia* infection.

From five days to one month after onset of *Yersinia* infection 17 patients (Table 1, Cases 1-17) developed acute anterior uveitis. The patients complained of redness, photophobia and pain, and some of them of diminution of vision and increased lacrimation. Pericorneal ciliary injection was observed in all patients; one patient (Case 6) with severe exudation into the anterior chamber and vitreous developed conjunctival chemosis. Aqueous flare and cells and fine keratic precipitates were constant findings (Table 2). Keratic precipitates were never mutton-fat. Marked vasodilation of the iris vessels was seen in four patients (Cases 6, 10, 11, and 15). On iris angiography, one of them (Case 11) showed vasodilation and fluorescein leakage in the nasal and superior parts of the iris (Fig. 1); the temporal half showed a dense iris nevus (Fig. 2), which occluded visualization of the iris vessels in angiography. Fibrinous exudation in the aqueous humor was seen in ten patients; one of them (Case 10) had hyperemia and petechial hemorrhages of the iris and on the next day hyphema was seen. In the acute stage, posterior synechiae developed in ten patients (Table 2). Hypertensive iridocyclitis and secondary glaucoma were never observed. Nine patients showed cells in the vitreous, and one of them (Case 7) punctate and snowball-like small, preretinal exudates in the inferior periphery. Six patients developed slight macular edema; cystic macular edema was not seen. One patient (Case 16) showed slight edema of the disk.

The uveitis was unilateral in 14 cases and bilateral in three (Table 3). The duration varied between three and 12 weeks (mean, 6.2 weeks). Topical medication with corticosteroids and cycloplegics sufficed in ten cases; in seven cases, because of fulminant onset of intraocular inflammation, systemic corticosteroids were used (Table 3). In eight cases uveitis recurred after a lapse of one month to three years (mean, 1.5 years). The duration of recurrences varied between two and 11 weeks (mean, 5.7 weeks). The inflammatory signs resolved completely in all patients.

Conjunctivitis occurred in nine patients: unilaterally in five and bilaterally in four (Table 4). In eight patients it occurred from four to 17 days after onset of abdominal symptoms; in five patients (Cases 4, 19-21, and 23) it coincided with arthritis and urethritis and in two (Cases 18 and 22) with arthritis. In one patient (Case 10) with no abdominal symptoms, conjunctivitis, arthritis, and urethritis occurred seven days after onset of fever. Conjunctivitis was mostly mild. The patient complained of redness and a burning sensation. No chemosis or follicles were noted except in a 29-year-old

TABLE 2

CLINICAL FEATURES OF UVEITIS ASSOCIATED WITH *YERSINIA* INFECTION*

Patient No.	Aqueous		Keratic Precipitates		Exudate	Posterior Synechiae	Increased IOP	Cells in Vitreous	Macular Edema	Edema of Disk
	Flare	Cells	Small	Mutton Fat						
1	+	+	+	−	−	+	−	+	−	−
2	+	+	+	−	+	−	−	−	−	−
3	+	+	+	−	+	+	−	+	−	−
4	+	+	+	−	+	−	−	−	−	−
5	+	+	+	−	−	−	−	+	+	−
6	+	+	+	−	+	+	−	+	+	−
7	+	+	+	−	+	+	−	+	−	−
8	+	+	+	−	−	+	−	−	−	−
9	+	+	+	−	+	+	−	+	+	−
10	+	+	+	−	+	+	−	+	+	−
11	+	+	+	−	+	+	−	−	−	−
12	+	+	+	−	−	−	−	−	−	−
13	+	+	+	−	+	+	−	−	−	−
14	+	+	+	−	−	+	−	+	+	−
15	+	+	+	−	−	−	−	−	−	−
16	+	+	+	−	+	−	−	+	+	+
17	+	+	+	−	−	−	−	−	−	−

*IOP designates intraocular pressure; + designates symptom was present; −, that symptom was absent.

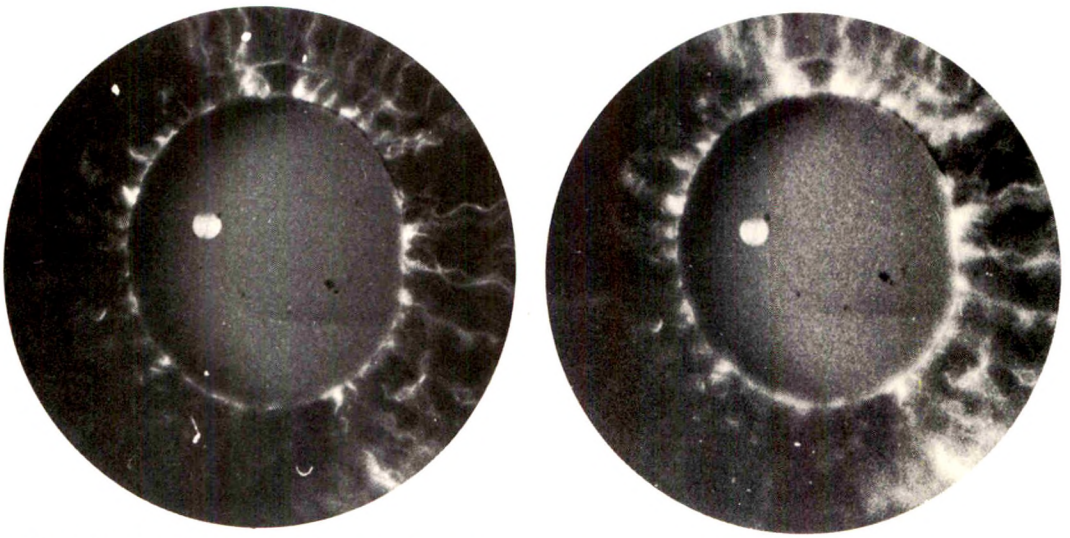

Fig. 1 (Saari and associates). Case 11. Right eye. Left, Iris angiogram showing vasodilation in nasal and superior parts of iris and early peripupillary leakage. Right, In later stage, diffuse leakage of iris vessels. No radial vessels are visible in the temporal half of the iris.

man (Case 22) with chronic blepharitis; two weeks after onset of abdominal symptoms he developed redness, chemosis, and enlarged follicles in the palpebral conjunctiva of the lower eyelids. In a severe case (Case 9) there were slight pain, palpebral edema, and purulent exudate. Keratitis was never seen. Conjunctivitis resolved spontaneously in seven days. In two patients (Cases 9 and 10) chloramphenicol-hydrocortisone ointment was given without any improvement. In three patients (Cases 4, 9, and 10) acute anterior uveitis occurred a few days after disappearance of conjunctivitis, and in one patient (Case 23) ten months later.

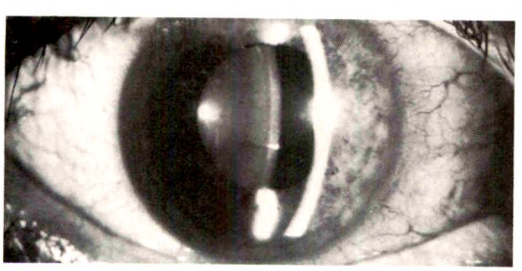

Fig. 2 (Saari and associates). Case 11. Right eye showing dense nevus in temporal half of the iris.

Twenty patients had infection with *Y. enterocolitica* serotype 3. The maximum titers varied between 160 and 20,000 (Table 5). Three patients had infection with *Y. enterocolitica* serotype 9; the maximum titers against this bacteria ranged from 640 to 5,120.

The peak erythrocyte sedimentation rate values varied between 18 and 148 mm/hr (mean, 73 mm/hr). The highest leukocyte counts were between 5,600 and 16,600/mm^3 (mean, 10,400/mm^3) (Table 5).

Latex test titers were persistently positive in one patient (Case 13) and in three patients (Cases 10, 11, and 18) they were positive during the acute stage of infection. Waaler-Rose and antinuclear antibody titers were negative in all patients. Antistreptolysin O titer was normal in all but Cases 9, 14, and 21 with positive antistreptolysin titers of 280, 800, and 600 respectively. HLA-B27 antigen was

TABLE 3

SIDE, DURATION, TREATMENT, AND RECURRENCE IN UVEITIS ASSOCIATED WITH *YERSINIA* INFECTION*

Patient No.	Side	Duration (wks)	Systemic Corticosteroids	Recurrent
1	U	6	+	+
2	B	5	−	−
3	U	7	−	−
4	U	5	−	−
5	U	5	+	+
6	U	6	+	+
7	U	12	−	+
8	B	6	−	+
9	U	9	+	−
10	U	9	+	−
11	B	5	−	+
12	U	3	−	+
13	U	6	−	+
14	U	5	−	−
15	U	4	−	−
16	U	6	+	−
17	U	6	+	−

*U designates unilateral; B, bilateral; + designates presence; −, absence.

found in all 17 patients tested (100%).

Four pedigrees of the families with cases of ocular inflammation associated with *Yersinia* infection and their family members with rheumatic diseases are shown in Figure 3.

In Family KA, the father had acute polyarthritis after *Yersinia* infection. One year later his son (Case 1) developed acute polyarthritis, urethritis, and unilateral acute anterior uveitis after *Yersinia* infection, with a recurrence of acute anterior uveitis two years later; he had sacroiliitis and HLA-B27 antigen.

In Family MA, the proband (Case 8) with seronegative rheumatoid arthritis for seven years and HLA-B27 antigen developed acute polyarthritis and bilateral acute anterior uveitis following *Yersinia* infection; she has had recurrent acute anterior uveitis twice in the left eye two months and two years later, respectively. Her mother had suffered from postdysenteric chronic Reiter's syndrome with recurrent joint symptoms.

In Family NI, two of the three sons had acute anterior uveitis; the third was healthy. The proband (Case 16) with HLA-B27 had acute polyarthritis and acute anterior uveitis after *Yersinia* infection. His younger brother with rheumatoid arthritis had had acute anterior uveitis three times.

In Family CA, the proband (Case 18) with HLA-B27 antigen developed unilateral conjunctivitis and acute polyarthritis after *Yersinia* infection; he and his two siblings had sacroiliitis and the father and one cousin had ankylosing spondylitis.

All members of one family consisting of father, mother, and one daughter contracted *Yersinia* infection with fever, diarrhea, and abdominal pain. Only the father (Case 4) with HLA-B27 developed conjunctivitis, acute anterior uveitis, reactive arthritis, and urethritis; the daughter,

TABLE 4

CLINICAL FEATURES OF CONJUNCTIVITIS ASSOCIATED WITH *YERSINIA* INFECTION*

Patient No.	Side	Conjunctival Injection	Chemosis	Follicles	Keratitis	Subsequent AAU	Arthritis	Urethritis
4	U	+	−	−	−	+	+	+
9	U	+	−	−	−	+	−	−
10	B	+	−	−	−	+	+	+
18	U	+	−	−	−	−	+	−
19	U	+	−	−	−	−	+	+
20	B	+	−	−	−	−	+	+
21	B	+	−	−	−	−	+	+
22	B	+	+	+	−	−	+	−
23	U	+	−	−	−	+	+	+

*U designates unilateral; B, bilateral; AAU, acute anterior uveitis; + designates symptom was present; −, that symptom was absent.

TABLE 5

LABORATORY FINDINGS IN PATIENTS WITH *YERSINIA* INFECTION AND EYE INFLAMMATION*

Patient No.	*Yersinia* Serotype	*Yersinia* Titer	Peak ESR (mm/hr)	Highest Leukocyte Count/mm³	Latex	Waaler-Rose	ANA	ASO	HLA-B27
1	Ye 3	5,120	45	9,700	−	−	−	−	+
2	Ye 3	2,560	68	7,800	−	−	−	−	+
3	Ye 9	640	70	11,600	−	−	−	−	+
4	Ye 9	1,280	41	11,600	−	−	−	−	+
5	Ye 3	10,240	49	10,900	−	−	−	−	+
6	Ye 3	1,280	76	9,900	−	−	−	−	+
7	Ye 3	640	50	10,100	−	−	−	−	+
8	Ye 3	10,240	62	6,400	−	−	−	−	+
9	Ye 3	320	46	10,300	−	−	−	280	NT
10	Ye 3	2,560	90	6,400	±	−	−	−	NT
11	Ye 3	3,200	116	7,800	±	−	−	−	NT
12	Ye 3	5,120	24	9,900	−	−	−	−	NT
13	Ye 3	2,560	57	11,900	+	−	−	−	+
14	Ye 3	320	75	5,600	−	−	−	800	+
15	Ye 3	160	148	12,100	−	−	−	−	NT
16	Ye 3	20,000	53	11,200	−	−	−	−	+
17	Ye 3	160	130	10,300	−	−	−	−	+
18	Ye 3	2,560	117	12,000	±	−	−	−	+
19	Ye 9	5,120	80	7,900	−	−	−	−	+
20	Ye 3	1,280	86	14,300	−	−	−	−	+
21	Ye 3	1,280	68	14,500	−	−	−	600	+
22	Ye 3	1,280	18	11,400	−	−	−	−	NT
23	Ye 3	160	118	16,600	−	−	−	−	+

* + designates positive or pathologic finding; −, that it was negative or absent; ESR designates erythrocyte sedimentation rate; ANA, antinuclear antibody titer; ASO, antistreptolysin O titer (>200); Ye, *Yersinia enterocolitica*; and NT, not tested.

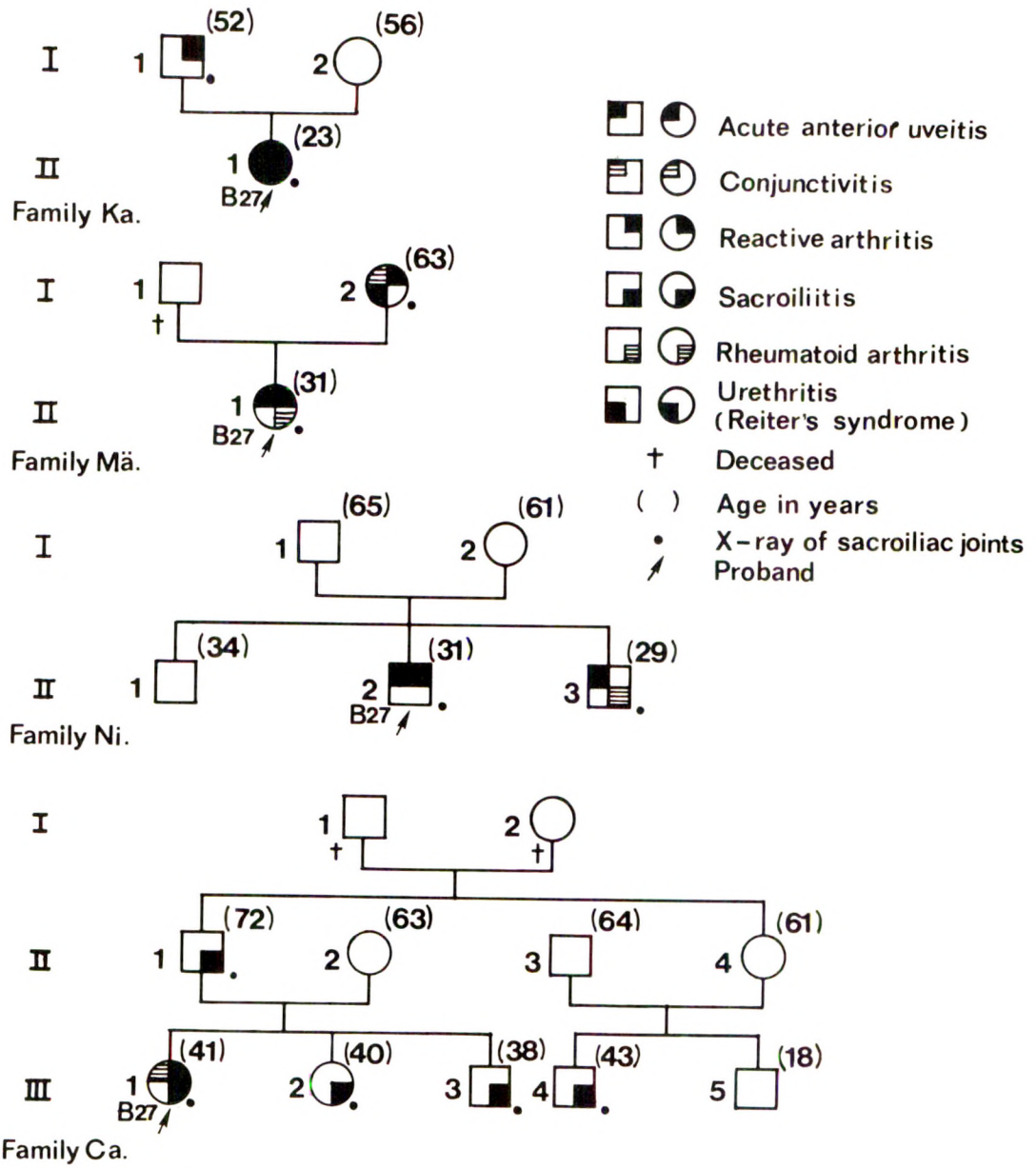

Fig. 3 (Saari and associates). Pedigrees of Families Ka., Mä., Ni., and Ca. showing probands with HLA-B27 and acute anterior uveitis or conjunctivitis associated with *Yersinia* infection, and rheumatic diseases in the same family.

who was HLA-B27 negative, and her mother did not develop any rheumatic disease.

Discussion

During the first month after onset of the disease our patients developed nongranulomatous acute anterior uveitis, unilaterally in 14 cases, with ciliary injection, photophobia and pain, aqueous flare, cells and often exudates, small keratic precipitates, and vitreous cells. Similar characteristics were seen in HLA-B27 associated[12,13] and familial[13,14] acute anterior uveitis. In this study vasodilatation and leakage of the iris vessels, macular edema, and in one case edema of the optic disk, were additional findings. Complete resolution of acute anterior uveitis occurred on the average during the first six weeks when corticosteroids were used, but there was a tendency to recurrence in about half of the patients during three years of follow-up.

Patients with acute anterior uveitis often have a high erythrocyte sedimentation rate caused by some systemic disease.[15,16] In our patients high erythrocyte sedimentation rates and leukocytosis occurred after *Yersinia* infection. Except for persistently positive latex test titers in one case, the patients had no IgM rheumatoid factor or antinuclear antibodies similar to HLA-B27 associated familial acute anterior uveitis in patients with arthritis.[14]

In this study there was a striking association between acute anterior uveitis, reactive arthritis, ankylosing spondylitis/sacroiliitis, Reiter's syndrome, and HLA-B27. Of the 17 cases with acute anterior uveitis, all 12 patients tested had HLA-B27, all except one had reactive arthritis, ten had ankylosing spondylitis or sacroiliitis, and seven patients had Reiter's syndrome. Additionally, three families of the patients with acute anterior uveitis resulting from *Yersinia* infection showed rheumatic diseases in the relatives including familial occurrence of acute anterior uveitis in one family. This coincides with the observations that in *Yersinia* arthritis ocular inflammation is associated with HLA-B27,[10] and that acute anterior uveitis occurs together with HLA-B27 associated rheumatic diseases,[14,17,18] which are unusually frequent in the relatives of acute anterior uveitis patients.[18] However, acute anterior uveitis occurring after *Yersinia* infection may manifest independently without any joint or urethral involvement (Case 9). These findings suggest that acute anterior uveitis, which here occurred after *Yersinia* infection, belongs to the HLA-B27 associated rheumatic diseases. These diseases include ankylosing spondylitis, sacroiliitis, Reiter's syndrome, spondylitis in association with psoriaris, ulcerative colitis, and Crohn's disease, and some forms of reactive arthritis, which seem to have an obvious tendency to cluster into the same families. However, further work is necessary for the elucidation of the detailed genetic background of acute anterior uveitis.[19]

The present patients provide the best examples of an association between acute anterior uveitis, HLA-B27, and an identified infective agent. Evidence for the participation of infective agents in acute anterior uveitis has in the past been circumstantial. Any organism or antigen that can cause inflammation elsewhere in the body can cause inflammation of the eye.[20] However, most of the possible etiologic causes of uveitis are ubiquitous antigens, and a large proportion of the population may have had contact with these antigens, so that separating previous antigenic exposure from active infection that causes disease is difficult.[20] The observations of an association between HLA-B27 and acute anterior uveitis[17] and of the familial occurrence of acute anterior uveitis[18] have shed further light on the pathogenesis of this disease. The triggering factor of

HLA-B27 associated acute anterior uveitis may be an infection, some antigen, or minimal trauma.[21] In this study *Yersinia* infection always preceded acute anterior uveitis, confirming the role of infecting agents in the pathogenesis of acute anterior uveitis. Consequently, it seems possible that the reactive iritis described by us here is comparable to that of reactive arthritis occurring after several known bacterial infections.

Conjunctivitis associated with *Yersinia* infection was generally mild without any chemosis, follicles, or keratitis, and resolved in one week without treatment. It coincided in six cases with arthritis and urethritis, and in two cases with arthritis. *Yersinia* infection can trigger Reiter's syndrome[6,7,10] and in these eight cases conjunctivitis may be one symptom of complete or incomplete Reiter's syndrome. In one patient (Case 9) mucopurulent conjunctivitis occurred seven days after abdominal symptoms without any joint or urethral involvement as an independent disease. However, different symptoms of Reiter's syndrome may appear alone or in different combinations simultaneously or at irregular intervals for even months or years. The association of conjunctivitis occurring after *Yersinia* infection in eight cases with arthritis, in two with sacroiliitis, in four cases with subsequent acute anterior uveitis, and in all tested patients with HLA-B27, would still implicate it either as an independent disorder or as a symptom of Reiter's syndrome with an HLA-B27 associated rheumatic disease. In this respect acute anterior uveitis and conjunctivitis occurring after *Yersinia* infection may be similar to their genetic background.

Summary

We studied characteristics of ocular inflammation associated with *Yersinia* infection in 23 patients. After an acute onset with fever, diarrhea, and abdominal pain, 22 patients developed arthritis, 11 patients developed myalgia, 11 patients developed Reiter's syndrome, 17 patients developed acute anterior uveitis, and nine patients developed conjunctivitis. Sacroiliitis was found in 12 patients. The patients had high erythrocyte sedimentation rates, leukocytosis, and lack of antinuclear antibodies and rheumatoid factor. All 17 patients tested had HLA-B27 antigen. The patients with acute anterior uveitis showed aqueous flare, cells, fine keratic precipitates, and often exudates, posterior synechiae, vitritis, and macular edema. Acute anterior uveitis was mostly unilateral and resolved during corticosteroids on the average during the first six weeks; recurrences were seen in about half of the cases. Conjunctivitis was generally mild with no chemosis, follicles, or keratitis; and it resolved in one week without treatment. Our results indicate that in HLA-B27 positive patients infective agents can trigger acute anterior uveitis or conjunctivitis, which often occur together with rheumatic diseases.

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OPHTHALMIC MINIATURE

Short sight. In this case the iris is contracted, and the cornea, which in long sight is too much flattened, is too convex or polarized; therefore spectacles of an opposite character, and with concave glasses, become necessary. Mice are said to be short-sighted; hence the affection has been termed myopia or myopiasis, literally "mouse-sight."

J.G. Millingen
Curiosities of Medical Experience
London, Richard Bentley, 1839

SMALL UNILATERAL FOVEAL HEMORRHAGES IN YOUNG ADULTS

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Retinal hemorrhages occur in many pathologic states of the retina and choroid.[1-6] Patients with otherwise normal eyes may sustain multiple retinal hemorrhages secondary to ocular trauma or injury to the head, torso, or limbs,[7] as well as after increased intrathoracic pressure (Valsalva maneuver),[8,9] childbirth,[10,11] and exposure to high altitudes.[12-14] Review of our records disclosed that during the past five years we have observed small, unilateral, foveal hemorrhages without coincidental underlying disease in nine healthy young adults. We describe the clinical features of a syndrome that have been characterized or discussed only anecdotally in previous published reports.

SUBJECTS AND METHODS

Of the individuals studied, five were men and four were women. Their ages ranged from 18 to 47 years with a mean of 25 years. The most frequent initial complaint was central scotoma or blurred vision (Table 1). Two of three patients who were available for specific questioning gave a history of weight lifting. A period of at least several hours passed after the exertion before the onset of symptoms. Two women were taking estrogen medication orally and in one case the symptoms occurred after ocular trauma. None of the patients had a known systemic disease.

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RESULTS

Initial visual acuities ranged from 6/6 (20/20) to 6/60 (20/200). All patients had a small unilateral hemorrhage, involving the right eye in five patients and the left eye in four patients. In each instance the hemorrhage was located in the foveal or perifoveal area, was solitary and flat, and ranged in size from a punctate spot to one-half disk diameter. The larger hemorrhages appeared to be under the internal limiting membrane but the punctate hemorrhages were difficult to localize, especially when they occurred in the foveola. Fluorescein angiography showed only blockage of choroidal fluorescence by the larger hemorrhages, without evidence of defects in the retinal pigment epithelium or the indication of a vascular abnormality. Normal foveal hypofluorescence masked the presence of small foveal hemorrhages. In two patients a complete blood cell count with differential, prothrombin time, and activated partial thromboplastin time were normal, and in one of them a platelet count was also normal.

Detailed follow-up information was available for six patients. In five, the visual acuity returned to normal with complete resolution of the hemorrhage documented on the record in two weeks to one month. The sixth patient failed to return for follow-up examination until six months later, at which time normal visual acuity and resolution of the hemorrhage were noted.

The initial fundus appearance of the patient in Case 2 with a subinternal limiting membrane foveal hemorrhage is shown in Figure 1. Resolution was nearly complete at 27 days (Figs. 2 and 3).

TABLE 1

CLINICAL CHARACTERISTICS OF PATIENTS*

Case No., Age (yrs), Sex	Original Complaint	Eye	History	Initial Visual Acuity R.E. and L.E.	Size of Hemorrhage (Largest Diameter)	Time to Normal Visual Acuity and Resolution of Hemorrhage
1, 33, M	Decreased acuity	R.E.	Denied trauma or exercise	6/60 (20/200) 6/6 (20/20)	1/2 Disk diameter	6 mos
2, 23, M	Sudden scotoma	R.E.	Denied drugs or bleeding diathesis	6/15 (20/50) 6/6 (20/20)	1/2 Disk diameter	1 mo
3, 19, F	N.A.	L.E.	N.A.	6/6 (20/20) 6/15 (20/50)	Punctate	N.A.
4, 21, F	Trouble focusing	L.E.	N.A.	6/6 (20/20) 6/12 (20/40)	1/3 Disk diameter	N.A.
5, 18, F	Scotoma	L.E.	Sudden onset; with oral contraceptives	6/7.5 (20/25)	1/5 Disk diameter	1 mo
6, 27, M	Swollen eye	R.E.	Blunt trauma to orbit (fist)	6/60 (20/200) 6/3 (20/10)	Punctate	N.A.
7, 30, M	Blurred vision	L.E.	Began weight-lifting	6/6 (20/20) 6/6 (20/20)	Punctate	2 wks
8, 24, M	Eye strain	R.E.	Jogging	6/12 (20/40) 6/6 (20/20)	Punctate	1 wk
9, 47, F	Scotoma	R.E.	Lifting heavy luggage, taking Premarin for menapausal symptoms	6/7.5 (20/25) 6/6 (20/20)	1/5 Disk diameter	2 wks

*N.A. designates data not available.

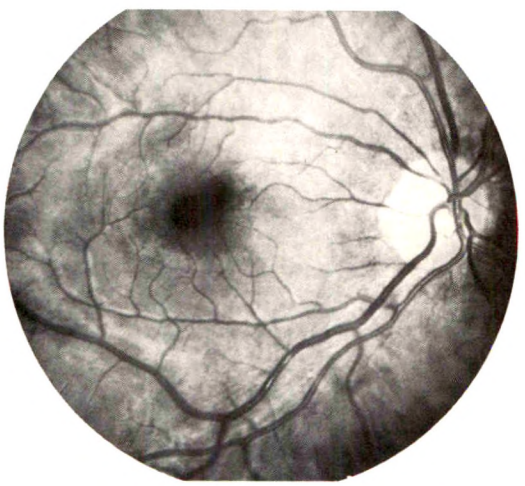

Fig. 1 (Pitta and associates). Foveal hemorrhage in the right eye of Patient 2.

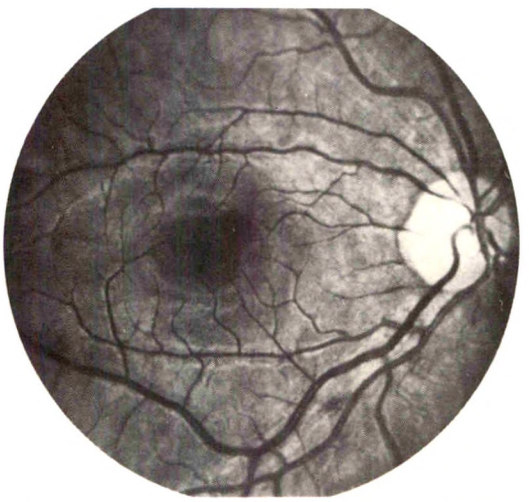

Fig. 2 (Pitta and associates). Resolving foveal hemorrhage at ten days in the right eye of Patient 2.

Figure 4 shows the subtle foveal hemorrhage in the patient in Case 7, who had the smallest hemorrhage in this series. His visual acuity was unaffected but a scotoma was noted. Goldmann contact lens examination after two weeks showed complete resolution of the lesion. Figure 5 shows the intermediate-sized hemorrhage in the patient in Case 9.

Discussion

Intraretinal macular hemorrhages in young adults may result from primary retinal disease, systemic disease, environmental and physiologic stress, or from

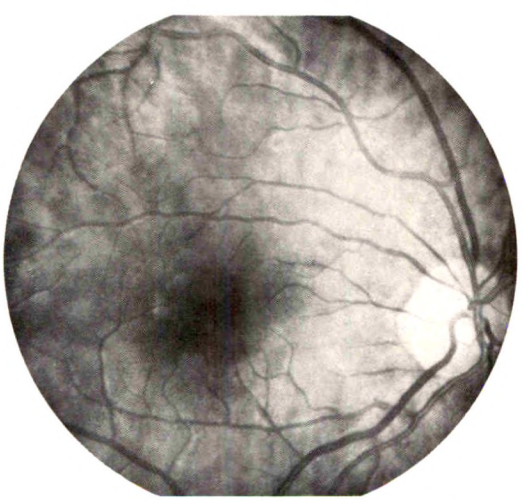

Fig. 3 (Pitta and associates). Nearly resolved foveal hemorrhage with return of normal visual acuity at 27 days in the right eye of Patient 2.

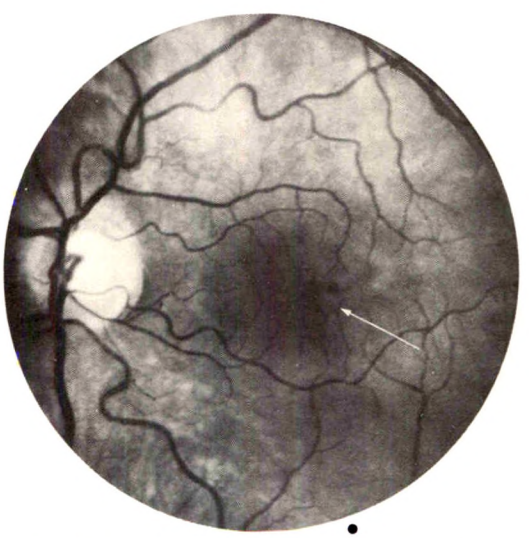

Fig. 4 (Pitta and associates). The smallest hemorrhage in this series, with normal visual acuity but a complaint of acute scotoma in the left eye with a punctate foveal hemorrhage (arrow).

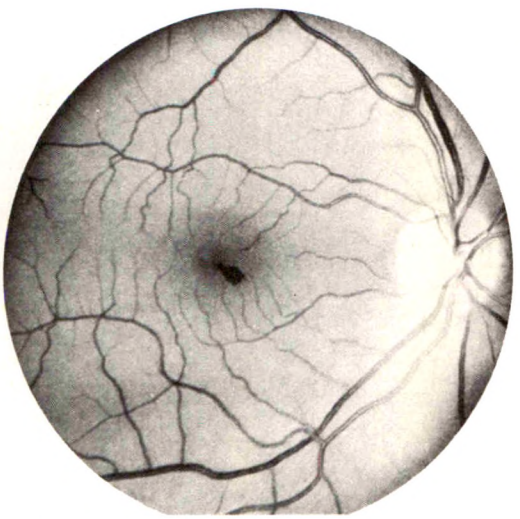

Fig. 5 (Pitta and associates). Intermediate sized hemorrhage in Patient 9 (red free photograph).

unknown causes. The macular hemorrhages that occur in ocular histoplasmosis, senile disciform degeneration, idiopathic choroidal neovascularization, angioid streaks, and severe myopia (Fuchs' spot) result from breaks in Bruch's membrane and subretinal neovascularization.[1-3] Familial occurrence of tortuous retinal vessels with macular hemorrhage has also been shown.[4,5] Retinal hemorrhages, often sparing the macula, may be seen in hypertension, diabetic retinopathy, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), toxic states (febrile and infectious diseases), cardiovascular shock (especially gastrointestinal hemorrhage), anticoagulant drug therapy, intracranial hemorrhage, and hematologic and hyperviscosity disorders.[6] None of the nine patients gave evidence of such disorders.

Direct trauma to the globe may cause choroidal, retinal, and vitreous hemorrhage in the injured eye, and indirect traumatic retinal angiopathy is also well documented as the result of injuries to the head, neck, chest, and long bones. Marr and Marr[7] reviewed Purtscher's retinopathy and attempted to differentiate it from fat embolism, traumatic asphyxia, and hydrostatic pressure injury from rapid deceleration, based on its signs, symptoms, and clinical course. Common to all such injuries, however, are multiple bilateral hemorrhages of various sizes up to one or more disk diameters, located in the posterior pole without predilection for the macula, and often accompanied by the soft exudates of capillary infarction. Also, traumatized patients usually have a variable loss of vision, which occurs slowly over a period of hours or days, and the hemorrhages and exudates resolve within several weeks with a gradual return of visual acuity to normal.

Duane[8] coined the term Valsalva hemorrhagic retinopathy for retinal hemorrhages apparently attributable to increased intrathoracic pressure caused by forceful exhalation against a closed glottis, or the physiologic equivalent, causing impaired venous return and increased intracranial venous pressure. He presented photographs of multiple preretinal hemorrhages in a patient after difficult endotracheal intubation. Similar hemorrhages have been observed after vomiting, violent coughing, arguments, and strenuous exertion, including gymnastics, weight lifting, and blowing up an air mattress.[8,9] These are usually large and often multiple retinal and preretinal hemorrhages and occur unilaterally or bilaterally in young adults without showing retinal abnormality. Visual acuity returns to normal within a few weeks.

Retinal hemorrhages that disappear rapidly are not unusual in the newborn. They may be located in the nerve fiber layer or deep retina, with an estimated incidence between 3 and 50% of vaginal births, but rarely occur in infants delivered by cesarean section. The hemorrhages resolve over days to weeks without known residual visual deficits.[10,11]

High altitude retinal hemorrhages have been shown to afflict Himalayan mountaineers from America but not native Sherpas.[12] These hemorrhages are generally found both in the peripapillary region and throughout the fundus at both preretinal and intraretinal levels of both eyes. They usually spare the macula and may be diffuse or punctate, confluent or flame-shaped.[13,14] Fluorescein angiography shows marked vessel tortuosity and dilation of both arterial and venous channels without leakage. The mechanism hypothesized is hypoxic endothelial decompensation with hemorrhage on exposure to increased retinal blood flow and increased venous pressure during vigorous exercise and rapid altitude change. Residual visual field defects have been reported.

In the present study punctate foveal hemorrhages occurred in one eye each of nine young adult patients, which were associated with a history of exertion in four cases, including weight lifting in two of the three patients available for specific questioning. Two women were taking oral estrogen medications. One patient had orbital trauma without other evidence of direct injury to the globe. The hemorrhages caused varying degrees of visual impairment from 6/6 (20/20) to 6/60 (20/200), but the visual acuity and fundus appearance returned to normal within several months in all cases available for follow-up. Fluorescein angiography failed to show other chorioretinal or vascular disease in any case. The hemorrhages were located either in the deep or superficial layers of the retina, and results of coagulation studies on two patients were normal.

This patient population, history, absence of primary chorioretinal disease, and good prognosis for rapid recovery correspond with earlier reports of retinal hemorrhages after exertion (Valsalva retinopathy). However, the pattern of unilateral solitary small hemorrhages limited to the fovea has not been shown in a previous series and differs from Duane's cases.[8] Gass[15] includes one such case, and Duane believes this pattern of hemorrhage is one manifestation of Valsalva retinopathy (personal communication, 1979). Four cases of idiopathic isolated macular hemorrhages in young adults have been discussed previously,[16,17] but photographs were not provided for comparison and abnormal coagulation studies were found in each case, although the nature of the coagulopathy was not defined. Another case of apparent spontaneous macular hemorrhage eventually evolved into a typical vitelliform degeneration.[16]

The differential characteristics of several hemorrhagic syndromes are shown in Table 2. Although the mechanism of solitary foveal hemorrhages is unknown, they may represent the minimum of a spectrum of retinal hemorrhages caused by sudden increase of venous back pressure. Because of their small size, similar punctate hemorrhages may not be seen if they occur outside the macular region or if they produce no visual symptoms even when located in the area of the fovea. During the five-year span of our series, no cases of typical Valsalva retinopathy as originally described by Duane were seen, and single punctate hemorrhages after exertion may be a much more common clinical problem than previously believed. There is no information to suggest a mechanism that would predispose them to occur unilaterally in the fovea.

Summary

We studied nine cases of single, small, intraretinal foveal hemorrhages in one eye each of nine young adults during the last five years. The patients ranged in age from 18 to 47 years and were otherwise healthy. Four patients gave a history of

TABLE 2

COMPARISON OF RETINAL HEMORRHAGES

	Unilateral Foveal Hemorrhage	Valsalva Retinopathy	High Altitude Retinal Hemorrhage	Newborn Retinal Hemorrhage	Purtscher's Retinopathy	Fat Embolism
History	Often exertion, oral estrogen medications	Valsalva maneuver	High altitude mountain climbing	Vaginal delivery	Chest compression	Fracture of long bones
Delay in onset	? hours	Often immediate	Days-weeks	Within one hour	1-2days	1-2 days
Visual acuity	Normal to 6/60 (20/200)	Variable	Often normal, may be 6/60 (20/200)	—	Variable	Often normal
External ocular examination	Normal	Normal	Normal	Normal	Normal, or subconjunctival hemorrhage	Normal, or petechial conjunctival hemorrhage
Ophthalmoscopic examination	Single, punctate to 1/2 disk diameter foveal hemorrhage, retinal	Multiple posterior pole hemorrhages, 1/2-2 disk diameters, retinal and preretinal	Solitary or multiple, punctate to confluent, retinal and preretinal	Solitary or multiple, small to large, retinal	Multiple exudates and small to large retinal and preretinal hemorrhages	Multiple exudates, occasional small retinal hemorrhages
Laterality	Unilateral	Unilateral or bilateral	Unilateral or bilateral	Unilateral or bilateral	Bilateral	Bilateral
Systemic signs	None	None	Mountain sickness (cardiorespiratory and neurologic)	None	Congestion and petechial hemorrhages of head, neck, upper torso	Systemic emboli
Recovery	Weeks-months	Weeks-months	Usually weeks-months; some residual electrophysiologic and field defects	Days-weeks	Weeks	Days

*Modified from Marr and Marr.[7]

strenuous exercise, most often weight lifting. The visual acuities ranged from 6/6 (20/20) to 6/60 (20/200) and most patients complained of a small central or paracentral scotoma. Fluorescein angiography did not show any retinal or choroidal vascular abnormalities and recovery of of visual acuity was excellent in all patients available for follow-up examination during a period of two weeks to six months.

ACKNOWLEDGMENTS

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SCLERAL BUCKLING PROCEDURE FOR RETINAL DETACHMENTS SECONDARY TO PROLIFERATIVE DIABETIC RETINOPATHY

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Retinal detachment caused by proliferative diabetic retinopathy characteristically develops late in the disease after contraction of the vitreous and associated adherent fibrous proliferations. Two types of retinal detachment are recognized, rhegmatogenous and tractional.

Rhegmatogenous retinal detachments are characterized by a convex contour, extension to the ora serrata, bullous and undulating surface, and one or more retinal breaks. Precise identification of retinal breaks is often difficult. The breaks may be hidden by fibrous proliferations, fixed retinal folds, or vitreous hemorrhage; they are often small, slit-like or oval, and may resemble a retinal hemorrhage.

Traction retinal detachments are caused by the contraction of the posterior vitreous surface and fibrous bands bridging the vitreous body and the retina. These detachments are characterized usually by the following: (1) a concave contour, (2) less subretinal fluid than rhegmatogenous detachments, (3) no extension anterior to the vortex ampullae, (4) greatest elevation at sites of vitreoretinal adhesions, and (5) absence of retinal breaks.

Three approaches to the therapy of retinal detachment caused by proliferative diabetic retinopathy have been attempted[1–10]: (1) scleral resection, (2) scleral buckling, and (3) vitrectomy.

Indentation or resection of the sclera may relax the vitreoretinal traction by reducing the distance between sites of vitreoretinal adhesion; vitrectomy releases the traction by severing the connection between these sites. In the rhegmatogenous detachments scleral buckling has been used in addition to close retinal breaks.

We evaluated 99 scleral buckling operations in 92 patients with retinal detachment associated with proliferative diabetic retinopathy.

SUBJECTS AND METHODS

The names of 165 inpatients seen here between 1965 and 1977 were cross-indexed for diabetic retinopathy, retinal detachment, and scleral buckling. Fourteen patients did not have detachments secondary to proliferative diabetic retinopathy. Twenty-two patients who had undergone scleral buckling surgery, but not as the primary procedure, were excluded (Table 1). Four patients with less than two months of follow-up were excluded. Seventeen of the patients with retinal detachments and proliferative diabetic retinopathy did not have a scleral buckling operation for the following reasons: vitrectomy performed instead of scleral buckling (four), high medical risk (three), surgery deemed not likely to succeed (three), small retinal detachment not requiring surgery (three), no retinal detachment on re-examination (one), or unknown (three). The number of patients who refused to undergo the recommended procedure is not known. The remaining 92 patients (99 operations) reflect our experience with the scleral buckling procedure for retinal detachments secondary to proliferative diabetic retinopathy during the 12-year period.

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TABLE 1

INITIAL PATIENT DATA

	No. of Patients
Total names obtained	165
Total charts located	151
Patients excluded	59
Nonproliferative diabetic retinopathy	14
Scleral buckling operation not primary procedure	22
No retinal detachment	2
Patients in whom scleral buckling was not performed	17
Patients with less than two months of follow-up	4
Patients included in study	92

Data extracted from the clinical record included the following for most cases: best corrected visual acuity, slit-lamp biomicroscopy of the anterior and posterior segment, applanation tonometry, direct and indirect ophthalmoscopy, Goldmann visual field, stereoscopic fundus photography, and fluorescein angiography.

Additional data obtained were the patient's age at the time of surgery, at the diagnosis of diabetes mellitus, and at the diagnosis of retinal detachment; sex; eye involved; nature of diabetic treatment; and previous photocoagulation. Fundus photographs and sketches were reviewed to judge whether fibrous proliferation or neovascularization predominated. The presence of preoperative and postoperative vitreous hemorrhage was noted. We evaluated the following preoperative characteristics of the detachment: detachment of the macula; extension to the ora serrata; and presence, characteristics, and location of retinal holes. Visual acuity was recorded before the onset of retinal detachment, at the diagnosis of retinal detachment, at its maximum improvement postoperatively, and at the most recent clinic visit. Visual acuity and pathological changes in the fellow eye were recorded.

Detachments with probable breaks with or without extension to the ora serrata were considered rhegmatogenous. All other detachments were classified as tractional, even though some had extension to the ora serrata.

The surgical techniques used included various combinations of explant material such as encircling tape, Silastic sponge, or grooved silicone piece. A Silastic sponge, usually in combination with an encircling band, was often used to close posterior retinal breaks. Subretinal fluid was drained whenever this procedure was considered safe. Five patients had scleral resection. Statistical analysis was done by the t test and χ^2 test. No allowance was made for multiple testing.

RESULTS

Of the 92 patients, 54 were women and 38 men (Table 2). Seventy-nine (86%) used insulin, 13 (14%) used oral hypoglycemics. In 57 patients (62%) diabetes was diagnosed before age 30 years (juvenile-onset; average age, 13.8 years), in 35 patients (38%) after age 30 years (adult-onset; average, 43.3 years) (Table 3). On the average, 18 years elapsed between the diagnosis of diabetes and the onset of retinal detachment in the adult-onset diabetics, and 23.1 years in juvenile-onset patients. Distribution between left and right eyes was similar, with seven patients requiring operations in both eyes.

TABLE 2

PREOPERATIVE DATA ON 92 PATIENTS

	No.	%
Sex		
Women	54	59
Men	38	41
Antidiabetic treatment		
Oral hypoglycemics	13	14
Insulin	79	86

TABLE 3

PATIENT AGE AT DIAGNOSIS OF DIABETES

	No. of Patients	Average Age at Diagnosis (yrs)
Age at diagnosis of diabetes		
Juvenile-onset (onset before age 30)	57	13.8
Adult-onset (onset after age 30)	35	43.3
Average number of years between diagnosis of diabetes and onset of retinal detachment		
Junvenile-onset	23.1	
Adult-onset	18.0	

Rhegmatogenous retinal detachments were seen in 53 eyes (54%) of 51 patients and tractional retinal detachments in 46 eyes (46%) of 44 patients. The peripheral limit of the detachment extended to the ora serrata in 34 of 46 eyes classified as tractional detachments.

A history or presence of vitreous hemorrhage was noted (Table 4) in 85 (86%) of the eyes. With the exception of two cases, the presence of vitreous hemorrhage did not prevent an adequate preoperative examination. All but one eye had some degree of posterior vitreous detachment.

The relative proportion of fibrous tissue and new vessels in the fibrovascular proliferations was assessed by reviewing the preoperative fundus diagrams and photographs, and the results were compared for the rhegmatogenous and tractional detachment groups (Table 5). This was done because of a clinical impression that a positive correlation existed between increased fibrous proliferation and tractional detachments. Fibrous tissue predominated more frequently in the tractional detachments (32/46, 70%) than in the rhegmatogenous detachments (20/53, 38%) and new vessels predominated more frequently in the rhegmatogenous detachments (11/53, 21%) than in the tractional detachments (3/46, 6%). Because fibrovascular proliferations evolve from an early predominantly vascular phase to a later predominantly fibrous phase, rhegmatogenous detachments probably tend to occur earlier, and tractional detachments later in the course of proliferative diabetic retinopathy.

TABLE 4

PREOPERATIVE STATUS OF THE VITREOUS

	No. of Eyes
Preoperative vitreous hemorrhage	
Present	85
Absent	14
Preoperative vitreous detachment	
Present	98
Absent	1

Although most of the retinal breaks (49/69, 71%) were located posteriorly within one to six disk diameters of the optic nerve, a number of breaks (20/169, 29%) were found seven or more disk diameters from the optic nerve (Table 6). Most of the breaks (44/69, 64%) were located temporally and most were round or oval and singular.

Nine eyes had breaks only anterior to the vortex vein ampullae. Although some of the more dramatic improvements in visual acuity occurred in this group, the anatomic and final visual acuity results were not significantly different from the remaining eyes.

The average follow-up was 38 months,

TABLE 5

PREOPERATIVE CHARACTERISTICS OF RETINAL FIBROVASCULAR PROLIFERATION

	Rhegmatogenous, No. of Eyes	Tractional, No. of Eyes
Fibrous tissue predominant	20	32
New vessels predominant	11	3
Fibrous tissue and new vessels equal	20	11
Fundus obscured	2	0

the median 36, and the mode 24 (range, two to 96 months) (Table 7). Seventy-three percent of the eyes were observed for more than one year postoperatively.

Twenty-five patients had earlier preoperative photocoagulation in the operated eye (14 xenon, nine argon, and two both xenon and argon). No difference was demonstrable in the results of this subgroup.

The most frequent complications in the immediate postoperative period were shallow anterior chamber (45 eyes), choroidal detachments (30 eyes), increased intraocular pressure (23 eyes), and vitreous hemorrhage (seven eyes) (Table 8). All complications were self-limiting, responsive to medical treatment, and without permanent sequelae.

Later complications included neovascular glaucoma (15 eyes), cataract formation (18 eyes), infected scleral buckling element (one eye), and conjunctival dehiscence (one eye).

Retinal redetachment occurred in 11 eyes (eight from the tractional group, three from the rhegmatogenous). The mean time after surgery was 14 months, with bimodal peaks at 4.8 and 31.5 months. All redetachments were operated on at least once, and one eye of the tractional group and one of the rhegmatogenous group required a second operation. The final anatomic and functional results after all

TABLE 6

CHARACTERISTICS OF RETINAL BREAKS

	No. of eyes (N=53)
Breaks per eye with rhegmatogenous detachments	
One	40
Two	13
Three	0
Four	1
Distance of break from optic disk (disk diameters)	(N=69)
1-2	7
3-4	27
5-6	15
7-8	4
9 or more	16
Type of retinal break	(N=69)
Round, oval hole	35
Slit, linear tear	8
Horseshoe tear	7
Lattice with hole	1
Operculated	1
Not characterized	17
Location of retinal breaks	(N=69)
Superior temporal quadrant	24
Inferior temporal quadrant	20
Superior nasal quadrant	12
Inferior nasal quadrant	8
Macula	5

TABLE 7

POSTOPERATIVE FOLLOW-UP*

Months After Surgery	No. of Eyes
2-5	7
6-9	9
10-12	11
13-24	20
25-36	8
37-48	14
49-60	10
61-72	12
73-84	6
85-96	3

*Mean, 38 months; median, 36 months; mode, 24 months.

TABLE 8

POSTOPERATIVE COMPLICATIONS IN 99 EYES

Type	No. of Eyes
Early	
Shallow anterior chamber angle	45
Increased intraocular pressure	23
Choroidal detachment	30
Vitreous hemorrhage during postoperative hospital stay	7
Corneal abrasion	6
Hyphema	2
Late	
Infected scleral buckle	1
Conjunctival dehiscence	1
Neovascular glaucoma	15
Cataract	17

reoperations did not differ significantly from the overall group.

Postoperative vitreous hemorrhage was seen in 59 eyes (60%) at some time after surgery. There was a statistically significant correlation between vitreous hemorrhage and final visual acuity (Table 9). Only 28 of 59 (48%) of the eyes with postoperative hemorrhage maintained visual acuity of finger counting or better at the final visit, as compared to 28 of 40 (69%) of those with hemorrhage. It was also statistically significant that of 42 eyes with visual acuity of hand motion or less at the final visit, 29 (70%) had postoperative hemorrhage, and, of the 17 patients with no light perception, 13 had postoperative hemorrhage. Choroidal detachments were not correlated with final visual acuity.

Both the anatomic and functional results were considered in assessing the operative success. The anatomic results were assessed by three criteria (Tables 10-12).

(1) Closure breaks. In 59 of 69 (86%) eyes the breaks were successfully closed (Table 10).

(2) Macular reattachment (Table 11). The macula was detached in 90 of 99 (91%) eyes preoperatively. Reattachment was achieved in 42 of 90 (46%) of these eyes, 26 of 48 (54%) in the rhegmatogenous group and 16 of 42 (38%) in the tractional. The difference between groups was not statistically significant at the $P = .05$ level.

(3) Postoperative compared to preoper-

TABLE 9

PREOPERATIVE AND FINAL VISUAL ACUITY

Visual Acuity	Vitreous Hemorrhage, % (N=59)	No Vitreous Hemorrhage, % (N=40)	Choroidal Detachment, % (N=30)	No Choroidal Detachment, % (N=69)	Total, % (N=99)
Change					
Better	27	45	33	35	34
Same	22	20	17	23	21
Worse	51	35	50	42	45
Final*					
6/6-6/12 (20/20-20/40)	5	2	4	4	
6/15-6/30 (20/50-20/100)	8	20	6	16	
6/48-6/60 (20/160-20/200)	5	7	10	4	
6/63-6/120 (19/200-10/200)	8	13	20	6	
6/133-6/240 (9/200-5/200)	5	7	0	9	
6/300-× (4/200-counting fingers)	17	13	17	15	
Hand motions	17	13	17	15	
Light perception	12	7	6	12	
No light perception	23	11	17	17	

*Percentage of patients with visual acuity of counting fingers or better: 58%; vitreous hemorrhage postoperatively, 48%; no vitreous hemorrhage postoperatively, 69%; choroidal detachment postoperatively, 60%; no choroidal detachment postoperatively, 56%.

TABLE 10

ANATOMICAL RESULTS

Retinal Breaks	No.
Retinal breaks present preoperatively	69
Breaks closed by surgery	59
New retinal breaks present postoperatively	8

ative extent of the retinal detachment (Table 12). This was classified as less, equal, or greater, based on the fundus drawing, fundus examination, photographs, sketches, and clinical notes. In 62 of 99 (63%) eyes the extent of retinal detachment was less postoperatively, 37 of 53 (70%) in the rhegmatogenous group, and 25 of 46 (54%) in the tractional. The difference between the rhegmatogenous and tractional groups was not statistically significant.

The functional results were assessed by comparing the preoperative visual acuity and the visual acuity at the last clinic visit (Table 13). The visual acuity was considered better if there was an improvement of at least one category which was usually at least halving of the visual angle, for example, 6/240 (5/200) to 6/120 (10/200).

Similarly, if the visual acuity worsened, usually at least doubling of the visual acuity angle, the visual acuity was considered worse. Light perception and hand motion were considered functionally equivalent categories, and any change within this group was considered the same. A decrease in the visual acuity from hand motions or light perception to no light perception was considered worse. Of the 99 eyes operated on, visual acuity was better in 33, the same in 15, and worse in 51. Improvement in visual acuity was more frequent in eyes with rhegmatogenous detachment (23/53, 43%) than in those with traction detachment (10/46, 22%). This was statistically significant at the P = .05 level.

TABLE 11

ANATOMICAL RESULTS IN PREOPERATIVE AND POSTOPERATIVE MACULAR DETACHMENT

Type of Retinal Detachment	Detachment of the Macula		
	No. Present Preoperatively	No. Present Postoperatively	No. Reattached
Rhegmatogenous	48	22	26
Tractional	42	26	16
Total	90	48	42

TABLE 12

EXTENT OF RETINAL DETACHMENT: POSTOPERATIVE COMPARED TO PREOPERATIVE STATUS

Type of Retinal Detachment	Less than Preoperative	Equal to Preoperative	Greater than Preoperative
Rhegmatogenous (N=53)	37	12	4
Tractional (N=46)	25	12	9
Total	63	24	13

TABLE 13

FUNCTIONAL RESULTS

Visual Acuity	Rhegmatogenous (N=53)	Tractional (N=46)	Total (N=99)
Change			
Better	23	10	33
Same	10	5	15
Worse	20	31	51
Final			
6/6-6/12 (20/20-20/40)	3	1	4
6/12-6/30 (20/50-20/100)	10	3	13
6/48-6/60 (20/160-20/200)	5	1	6
6/63-6/120 (19/200-10/200)	5	5	10
6/133-6/240 (9/200-5/200)	2	4	6
6/300-counting fingers (4/200)	10	7	17
Hand motions	7	8	15
Light perception	6	4	10
No light perception	4	13	17
Counting fingers or better: total 58%			
Operated vs nonoperated eye*			
Operated eye better			21
Operated eye the same			4
Operated eye worse			15

*N=85; seven patients who had bilateral operations were excluded.

Visual acuity of finger counting or better was recorded in all eyes assessed before the onset of retinal detachment (a predetachment observation was available in 57 of the 92 patients), 80 eyes at the time of detachment, and 57 at the last clinic visit, the latter representing 36 of the rhegmatogenous and 21 of the tractional detachments.

Visual acuity was recorded for all patients six months postoperatively, at which time 27 were better, 33 the same, and 39 worse. At the time of final visual acuity measurement 34 were better, 15 the same, and 50 worse.

Best postoperative visual acuity and its time relationship to the scleral buckling procedure were recorded (Table 14). In 24 (25%) eyes, best visual acuity was achieved within one month of the operation, in 47 (48%) within three months, in 63 (65%) with six months, and in 83 (82%) within the first year. These data indicated a progressive improvement in visual acuity in many eyes during a one-year period.

Initial and final visual acuity is tabulated for all 99 eyes (Fig. 1), for the tractional retinal detachments (Fig. 2), and for rhegmatogenous detachments (Fig. 3).

Eighty-five patients had unoperated fellow eyes; 42 of the 85 unoperated eyes

TABLE 14

TIME OF BEST POSTOPERATIVE VISUAL ACUITY

Months after Surgery	No. of Eyes
1	24
2	9
3	14
6	16
9	6
12	11
24	8
36	2
48	2
60	4
72	1
84	1
Mean, 10.9 mos	
Median, 4 mos	
Mode, 1 mo	

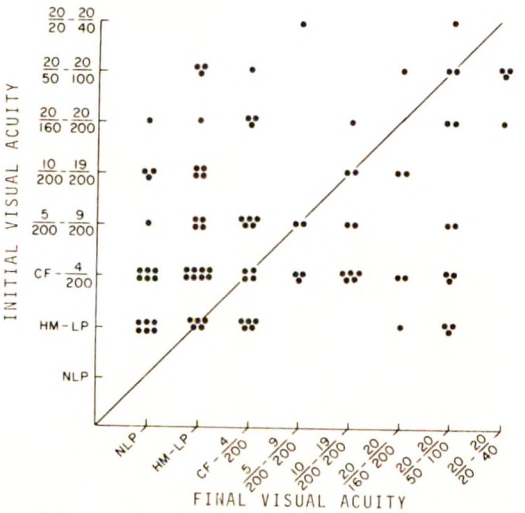

Fig. 1 (Miller and associates). Initial and final visual acuity in all eyes. Points on or above the diagonal represent eyes with worse visual acuity postoperatively compared with preoperatively as defined by an increment of one division on the graph which, in general, corresponds to a doubling of the visual angle. Likewise, points below the diagonal represent eyes with improved visual acuity. CF designates counting fingers; HM-LP designates hand motion-light perception (which were considered equivalent); NLP designates no light perception.

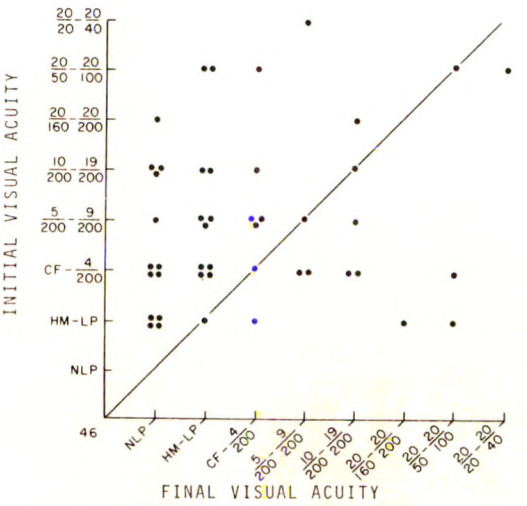

Fig. 2 (Miller and associates). Initial and final visual acuity in eyes with tractional retinal detachment.

had some degree of retinal detachment. In 37 of the 42 eyes , detachment was of the tractional type, was localized, and did not extend to the ora serrata. The remaining five eyes were considered rhegmatogenous because of the presence of a hole. At the most recent visit, visual acuity was finger counting or better in 55/85 (65%) of these 85 fellow eyes, 6/30 (20/100) or better in 34/85 (39%). In 21/85 (24%) of patients, the operated eye was the better seeing eye (Table 13) at the time of the last visit; 31/85 (60%) of the unoperated eyes were better.

Discussion

The criteria for anatomic and functional success usually applied to idiopathic rhegmatogenous detachment did not seem entirely applicable to retinal detachment associated with proliferative diabetic retinopathy.[1-8] Localized residual detachment may remain postoperatively even though the posterior pole is reattached and any retinal breaks that may have been present are closed. We considered three criteria for anatomic success: (1) closure of retinal breaks in 59 of 69 (86% success); (2) macular reattachment in 42 of 90 (46%) (26/48 [54%] of the rhegmatogenous, 16/42 [38%] of the tractional); and (3) decrease in extent of de-

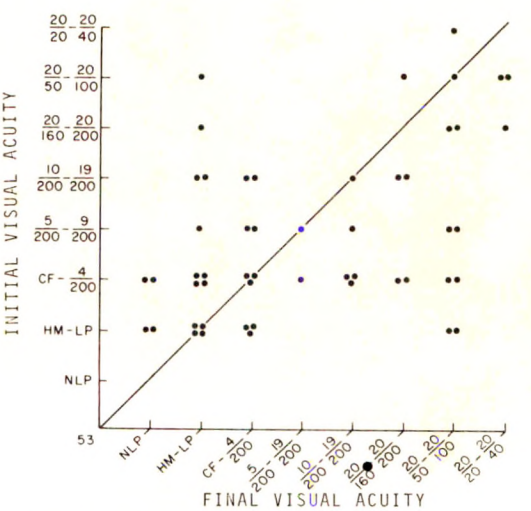

Fig. 3 (Miller and associates). Initial and final visual acuity in eyes with rhegmatogenous retinal detachment.

tachment, 62 of 99 (63%) (37/53 [70%] rhegmatogenous, 25/46 [54%] tractional). Macular reattachment seems the best criterion for anatomic success. Obscuration of fundus detail by lens opacities or vitreous hemorrhage as well as preretinal gliotic tissue may make this determination difficult.

Functional results were measured as the percentage of patients with improvement of visual acuity (in general, halving or less of the visual angle); 33/99 (34%) were considered improved, 58/99 (58%) maintained finger counting or better visual acuity, with rhegmatogenous detachments doing statistically better than tractional detachments in this respect.

Perhaps maintenance of visual acuity of finger counting is a reasonable criterion of success because with this level of vision the patient may be able to function independently in familiar surroundings.

We compared this series of cases with other reports (Table 11). However, each report may have unique inclusion and exclusion criteria and varying anatomic and functional criteria for success.[11] For example, inclusion of cases with imminently threatened[4] macular detachment would influence final results because some focal tractional detachments seem to remain stable for long periods of time. Likewise, it seems reasonable to exclude cases with extensive preretinal fibrosis,[4-9] excessive amount of vitreous blood or longstanding detachments. But how many of such cases were excluded? What was their eventual outcome? How frequent is spontaneous regression? Do the cases included from the varying reports have a similar degree of fibrotic or neovascular tissue?

Success criteria also vary. Visual acuity that changes from light perception to hand motion[10] barely seems an improvement. Plotting of preoperative as compared to postoperative visual acuity[6,9] gives a better overview of results than a summary percentage of those with a final visual acuity of finger counting.

The criteria for anatomical success also

TABLE 15

SUMMARY OF REPORTS OF PROLIFERATIVE DIABETIC RETINOPATHY, RETINAL DETACHMENT, AND SCLERAL BUCKLING

Study	Total Cases	Total Eyes	Sex (M/F)	Average Follow-up Mos	Retinal Reattachment	Postoperative Visual Acuity Counting Fingers or Better, %
	Rhegmatogenous/Tractional				Rhegmatogenous/Tractional	
Gragoudas and McMeel[9]	48	50/0	22/26	33	37 (74%)/—	25(67*)
Boniuk, Okun and Johnston[4]	—	34/47	—	6-72	—	54(67†)
Okun and Fung[2]	—	19/29	—	30	—	33(66†)
McMeel[1]	11	11/0	—	6-48	82/0	—
Wetzig[10]	—	0/60	—	6-108	‡	§
Tasman[7]	29	18/15	40/19		‖	
Panarelle[6]	17	—	—	24	—	82
Present study	92	53/46	38/54	38	¶/¶	58#

*67% of surgical successes - preoperative vs last postoperative visual acuity plotted only for 37/48 eyes with anatomical reattachment.

†At least three fourths of retina is reattached.

‡Improved, 25 (42%); unchanged, 14 (23%); worse, 21 (35%).

§Extent of retinal detachment postoperatively: rhegmatogenous, 70%; tractional, 54%; improved, 34% (see text).

‖No surgery. Five underwent spontaneous reattachment.

¶Breaks closed: rhegmatogenous, 86%; macula reattachment: rhegmatogenous, 54%, tractional, 38%.

Improved, 16(27%); worse, 26(43%).

vary. For example, localized areas of detachment caused by vitreoretinal traction may persist postoperatively, even though the posterior pole is reattached and retina breaks closed. Such an eye should not be considered a failure. Conversely, to consider an eye as a success because at least three-fourths of the retina is reattached[4] or only a small, stable traction detachment remains[9] may not be valid if the macula remains detached.

Our use of scleral buckle for treatment of nonrhegmatogenous retinal detachments secondary to proliferative diabetic retinopathy originated when this procedure was one of few reasonable alternative to manage this difficult clinical situation. In general, we use a scleral buckle for rhegmatogenous retinal detachments in which the retinal hole is not so far posterior as to preclude safe operative closure. If reattachment does not occur, then vitrectomy is done as a second procedure. Vitrectomy alone or supplemented in some cases with scleral buckling is performed for nonrhegmatogenous detachments involving the macula.

Although the vitrectomy procedure can be an effective method of treatment for both nonrhegmatogenous and rhegmatogenous detachments, the potential for serious complications with this intraocular procedure is substantial; the use of the scleral buckling procedure is safer and can be effective in carefully selected rhegmatogenous cases.

Summary

Ninety-two patients (99 eyes) underwent scleral buckling procedures for retinal detachment associated with proliferative diabetic retinopathy. Fifty-three procedures were for rhegmatogenous retinal detachment and 46 for tractional retinal detachment. The average follow-up period was 38 months.

Anatomic success was assessed in terms of closure of retinal breaks (59/69, 86%), macular reattachment (42/90, 46%), and reduction in extent of retinal detachment postoperatively as compared to preoperatively (62/99, 63%).

The visual acuity was better postoperatively in 33/99 (34%) of the eyes; 58/99 (58%) of the eyes maintained finger counting visual acuity.

Improvement in visual acuity was more frequent in eyes with rhegmatogenous detachment (23/53, 43%) than in those with traction detachment (10/46, 22%).

Although improvement is generally limited, some patients are markedly benefitted by scleral buckling procedures.

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OPTIC NERVE HYPOPLASIA ASSOCIATED WITH ABSENT SEPTUM PELLUCIDUM AND HYPOPITUITARISM

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Optic nerve hypoplasia is a developmental anomaly of the retina and optic nerve, previously believed to be an extremely rare phenomenon. This condition may be misdiagnosed as optic atrophy, but optic nerve hypoplasia, unlike many cases of optic atrophy, is a static condition.

In 1956, de Morsier[1] reported 36 cases of anomalies of the midline structure of the brain associated with abnormalities of the optic nerve, optic chiasm and optic tracts, and he called this condition "septo-optic dysplasia." This anomaly typically is composed of agenesis of the septum pellucidum and malformation of the fornix that fails to attach to the corpus callosum. The association of septo-optic dysplasia and hypopituitary dwarfism was first reported by Hoyt and associates.[2]

We describe five children with optic nerve hypoplasia, absent septum pellucidum, and hypopituitarism. To the best of our knowledge these are the first published cases in which computed axial tomograms are used for the diagnosis of absent septum pellucidum in children with this syndrome.

CASE REPORTS

Case 1—A 5 1/2-year old first-born boy was first seen in the Ophthalmology Clinic here on Sept. 18, 1975. He was born to a 21-year-old woman on Feb. 1, 1970. Family history was noncontributory. He had prolonged neonatal jaundice of unknown cause until age 3 months.

At age 5 months a diagnosis of de Morsier's syndrome was made because of small optic disks and a pneumoencephalogram that revealed diffuse cortical hypoplasia, moderately enlarged lateral ventricles, and absence of the septum pellucidum.

At age 5 1/2 years the child was being examined for fever to 38.9°C on numerous occasions without other symptoms or signs of infections. Serum sodium was in the range of 148 to 165 mEq/l without polydipsia.

Ophthalmological examination revealed visual acuity of no light perception in both eyes; pupils were 4 mm in both eyes and sluggishly reactive to light. Motility examination revealed an exotropia of 30 prism diopters by Hirschberg and mild symmetrical pendular nystagmus in both eyes; intraocular pressure was normal to palpation in both eyes. Ophthalmoscopic examination revealed bilateral optic nerve hypoplasia (Fig. 1). Other findings on physical examination were as follows: height at the 16th percentile for his age; weight at the 78th

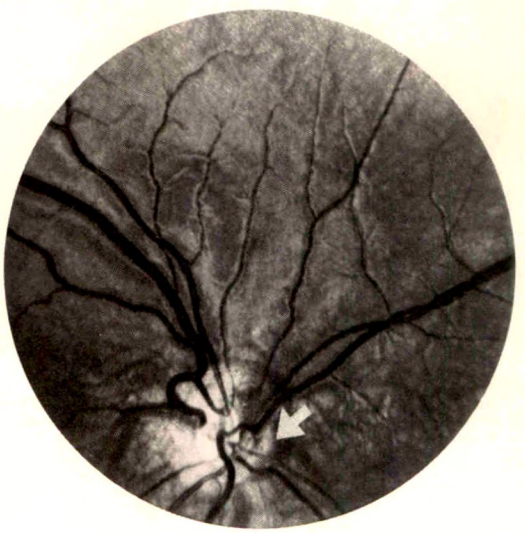

Fig. 1 (Krause-Brucker and Gardner). Case 1. Right eye, Hypoplastic disk, yellow peripapillary cuff and pigmented nasal crescent called the double ring sign. Note edge of the optic disk (arrow) and prominent optic cup.

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percentile; head circumference at the 50th percentile; and developmental retardation. Chromosome studies were normal (46 XY). Endocrine studies revealed that the child had diabetes insipidus, hypothyroidism, growth hormone, and adrenocorticotropic hormone deficiency (Table 1).

The child has been treated with hydrocortisol, sodium levothyroxine, and chlorpropamide for diabetes insipidus. His bone age is advancing chronologically, his height is approaching the 50th percentile, and his diabetes insipidus is well controlled.

Case 2—A 3-year-old first-born boy was first seen here on Jan. 10, 1977. He was born on Nov. 29, 1973. Labor and delivery were normal. Birth weight was 4,288 g. He was jaundiced for a few days after birth but the jaundice spontaneously regressed. At age 2 months iron deficiency anemia was diagnosed and treated. Subsequently at Oakland Naval Hospital, de Morsier's syndrome was diagnosed, including absence of the septum pellucidum shown by pneumoencephalography. A water deprivation test showed diabetes insipidus and thyroid function tests were normal. At that time, however, head circumference was small with height and weight both greater than the 90th percentile.

At the time of the child's visit here, he had a history of excessive water intake. Medical history also included recurrent serous otitis media and delayed developmental milestones. Family history revealed a maternal grandmother with diabetes mellitus and the older of two siblings had surgically treated intussusception.

Ophthalmological examination showed visual acuity of light perception in both eyes, and the child did not grasp for large objects. Motility examination revealed that the eyes would deviate upward and there was horizontal pendular nystagmus increasing on right gaze; extraocular muscle movements were normal and an esotropia of 20 prism diopters Krimsky was present; pupils were equal and reacted to light with no Marcus Gunn pupillary response; retinoscopy after using 2% cyclopentolate HCl and 10% phenylephrine was −1.25 +1.00 ×105 in the right eye and −1.00 +1.00 ×75 in the left eye.

TABLE 1

PITUITARY FUNCTION STUDIES

	Normal Values	Case 1	Case 2	Case 3	Case 4	Case 5
Antiduretic hormone						
Water deprivation						
Baseline urine osmolarity	(mOsm/kg of water)	261	158		804	110
6 hr		393	255		769	686
1 hr after Pitressin		619	499		751	
Thyroid studies						
Tetraidothyronine (T4 [Murphy Pattee])	3.3-8.9 μg/dl	2.4	5.6	8.4	5.6	4.5*
Serum thyroxine iodine by radioimmunoassay	2.5-7.5 μg/dl	3.2 7.4			5.3	4.5
Thyroid stimulating hormone	Up to 10 μμ/ml	31.5	3.5		6	12.4
Growth hormone						
Stimulation test levodopa						
Baseline	♂0-8 ng/ml	1.9		1.05		<1.00
90 min	>(7-10) ng/ml	1.0		1.02		
After arginine infusion						
Baseline		1.2	2.71	<1.00	<1.00	<1.00†
End infusion	>(7-10) ng/ml	1.9	2.76	1.12	<1.00	<1.00†
Insulin induced hypogylcemia						
Baseline			1.22	<1.00	<1.00	
Maximum response	>(7-10) ng/ml		2.71	<1.00	<1.00	
Adrenocorticotropic hormone						
11 desoxycortisol (compound S)	0.05-0.25 μg/100ml	0.5				
8 hrs after metyrapone		1.1	2.0		0.9	3.2
Serum cortisol baseline (A.M. values)	AM7-25 μg/dl MP2-9 μd/dl	1.0	1.9	16.3	6.0	<1.00
8 hrs after metyrapone		0.4			2.4	2.1
Insulin induced hypoglycemia						
Serum cortisol maximum response	>16		14.9	22.7	4.2	9.3‡

*Normal values changed to 5.0-13.0 μg/dl.
†Serum glucose equals 45 mg/100 ml.
‡No insulin given because serum glucose equals 42 mg/100ml.

Ophthalmoscopic examination revealed bilateral marked optic nerve hypoplasia. Other findings were as follows: head circumference two standard deviations below normal, height between third and tenth percentile and weight at the 50th percentile; a wide, extended gait and calcaneous valgus; psychological testing indicated a 1 ½- to 2-year-old level; and a mild conductive hearing loss bilaterally. Laboratory studies showed hypoproliferative type anemia, diabetes insipidus, normal thyroid function, growth hormone deficiency, and adrenocorticotropic hormone deficiency (Table 1).

Radiologic studies showed a bone age (Grulich Pyle) of 24 months as compared with chronologic age of 37 months and computed axial tomography showing partial absence of the septum pellucidum (Fig. 2). The child is presently being treated with growth hormone.

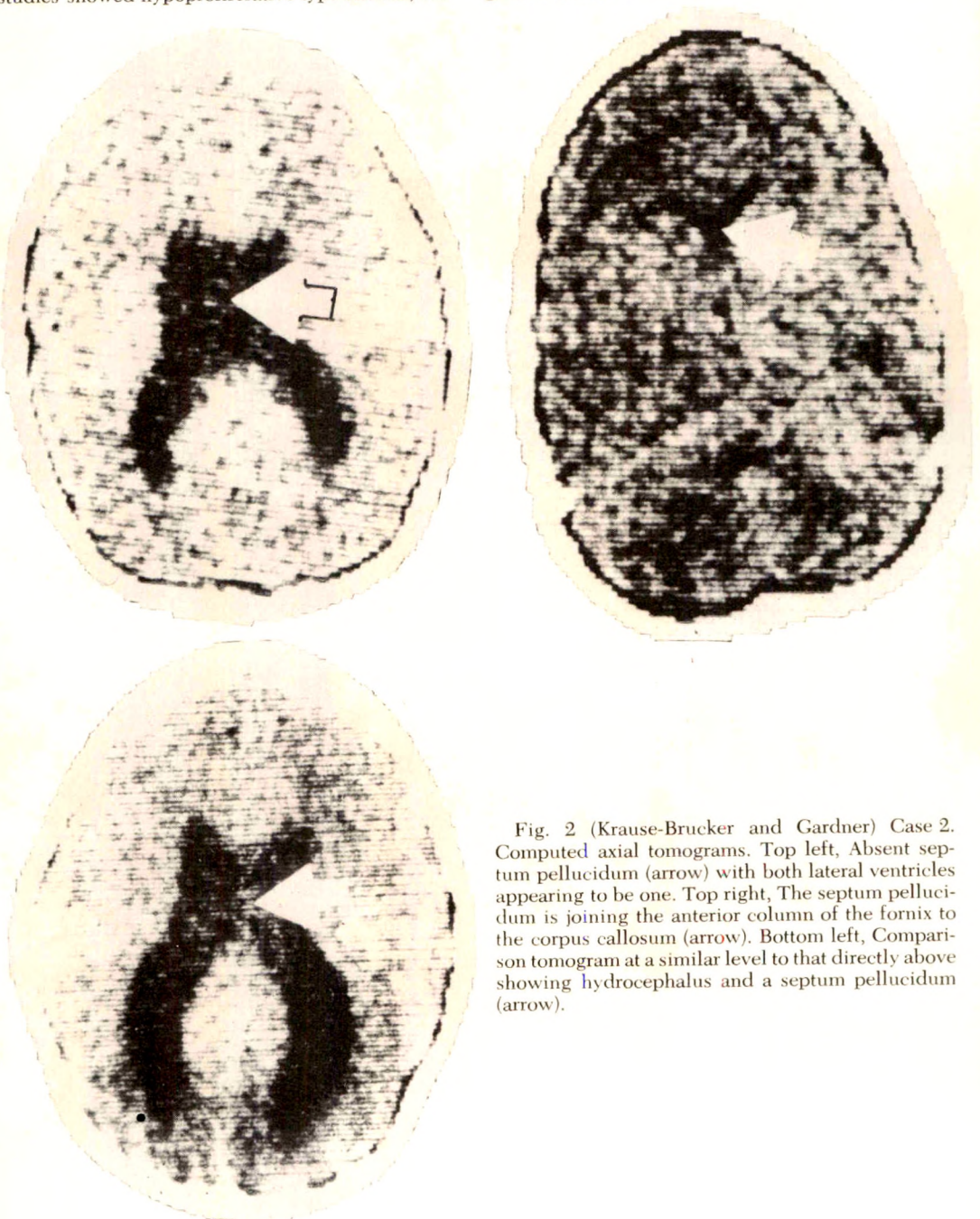

Fig. 2 (Krause-Brucker and Gardner) Case 2. Computed axial tomograms. Top left, Absent septum pellucidum (arrow) with both lateral ventricles appearing to be one. Top right, The septum pellucidum is joining the anterior column of the fornix to the corpus callosum (arrow). Bottom left, Comparison tomogram at a similar level to that directly above showing hydrocephalus and a septum pellucidum (arrow).

Case 3—A 6-year-old first-born boy of apparently normal intelligence had been followed up here since age 1 ½ years. The patient was delivered by caesarian section on June 3, 1970, because of cephalopelvic disproportion. The first trimester of pregnancy was complicated by a urinary tract infection, treated with an unknown antibiotic. The postnatal course was uneventful. Family history revealed that a maternal uncle had diabetes mellitus, a maternal great grandmother was blind, cause unknown, and a paternal uncle had esotropia.

When the boy was about one month old the parents noted he had strabismus and poor ocular following movements. At 3 ½ months of age, a diagnosis of bilateral optic atrophy and pendular nystagmus was made.

The child was first seen in the ophthalmology clinic at age 17 months, at which time he was being examined for psychomotor retardation. Electroencephalography results were consistent with a seizure disorder. Results of ophthalmologic examination were as follows: the child fixed and followed objects with either eye, better with the left eye than the right eye; 40 to 50 prism diopters of esotropia were noted; cycloplegic refraction was +1.00 sphere for both eyes; and bilateral optic nerve hypoplasia was noted. Results of optic foramina plain roentgenograms were normal.

At age 22 months the patient was examined because of polyuria. At that time water deprivation studies showed a baseline urine specific gravity of 1.006 to 1.017. A diagnosis of diabetes insipidus was made, and vasopressin (Pitressin) was started intramuscularly.

At age 3 years a trial of patching of the left eye was initiated because of poor fixation of the right eye. After six months patching was stopped because fixation failed to improve. Visual acuity at that time was 3/30 (10/100) in the left eye, using Allen cards. The right eye could not be evaluated because of poor fixation. He was lost to follow-up in the ophthalmology clinic after age 4 years.

At age 6 years the child was examined because of delayed bone age and failure to grow, his height being greater than three standard deviations below the mean. Endocrinologic studies showed normal thyroid and adrenal function and absent growth hormone (Table 1). Computed axial tomography performed Oct. 1, 1976, showed an absent septum pellucidum, which confirmed the diagnosis of septo-optic dysplasia (Fig. 3). Computed axial tomography of the orbit and optic nerve views showed no evidence of asymmetry, but accurate measurements of the size of the optic nerves could not be obtained. The child is awaiting growth hormone treatment.

Fig. 3 (Krause-Brucker and Gardner). Case 3. Computed axial tomography. Tomograms at levels similar to those pictured in Figure 2 showing complete absence of the septum pellucidum.

Case 4—A 10-year-old boy has been followed up here since his birth on March 25, 1976. The child's mother took an unknown nonprescription medication during her pregnancy. Labor and delivery were normal. Birth weight was 2,954 g. At age 5 hours the child became cyanotic, had a mild seizure, and decreased respirations. A diagnosis of hypoglycemia, serum glucose dropping to 6 mg/100 ml at one time and hyperbilirubinemia-serum bilirubin as high as 21 mg/100 ml was made.

At age 1 month the child was examined for persistent jaundice, a seizure, and failure to thrive. No cause for the jaundice was found. Results of tests including VDRL, cephalin flocculation, urine for inclusion bodies, lumbar puncture, protein bound iodine, *Toxoplasma* dye test, stool trypsin, a rose bengal liver scan, amino acid screening, and electroencephalography were all normal. The right eye showed an amaurotic pupillary response and hypoplasia of the right optic nerve.

At age 3 ½ years 30 to 50 prism diopters of alternating esotropia was noted on fixing and following with either eye. Cycloplegic refraction after instillation of atropine, phenylephrine, and cyclopentolate was −4.50 +1.25 ×180 in the right eye and −4.50 +.75 ×180 in the left eye. At age 4 years both optic nerves were first noted to be hypoplastic; the right disk was paler than the left. At age 6 years a diagnosis of Legg-Calvé-Perthes disease and bilateral clinodactyly was made.

At age 9 ½ years the child was examined for growth retardation. Height and weight were both less than the 3rd percentile for his age; I.Q. Wechsler was between 50 and 70. Karyotype was normal. Endocrine studies showed growth hormone deficiency, adrenocorticotropic hormone deficiency, normal thyroid, and posterior pituitary function (Table 1). Results of skull roentgenograms were normal, but computed axial tomography showed absence of the septum pellucidum. A diagnosis of septo-optic dysplasia was made.

Ophthalmologic examinations at age 9 ½ and 10 years revealed best corrected visual acuity was R.E.: 6/30 (20/100) and L.E.: 6/60 (20/200). Cycloplegic refraction again showed myopia. Pupils were 4 mm in both eyes and reacted to light; 50 prism diopters of right esotropia and horizontal pendular nystagmus least with the patient's head rotated 10 to 15 degrees to the left were noted. Intraocular pressure was normal to palpation. Results of slit-lamp examination were normal. Ophthalmoscopic examination again revealed bilateral optic nerve hypoplasia; the right disk was smaller than the left. The child is presently being treated with human growth hormone and cortisol.

Case 5— A 7-month-old first-born boy was referred to the ophthalmology clinic because of oculogyric movements bilaterally. The child was born on Sept. 28, 1977. Labor and delivery were normal. Birth weight was 3,919 g, length 53 cm, and head circumference 36 cm. Postnatal course was unremarkable except for mild icterus treated with phototherapy. Family history was noncontributory.

Ophthalmologic examination revealed that the child did not fix or follow a bright light. The right pupil did not react to light and had a positive Marcus Gunn pupillary response, the left pupil reacted to light. Motility examination revealed pendular nystagmus with jerk nystagmus to the left occasionally. Ophthalmoscopic examination revealed bilateral optic nerve hypoplasia.

At this time, his height was 75th percentile for his age, weight 90th percentile, and head circumference 95th percentile. The rest of the physical examination was unremarkable except for small male genetalia.

Computed axial tomography showed absence of the septum pellucidum and a widened anterior subarachnoid space, confirming the diagnosis of septo-optic dysplasia.

Endocrinologic studies showed growth hormone deficiency and adrenocorticotropic hormone deficiency (Table 1). Posterior pituitary function was normal, thyroid function was equivocal, Tetraiodothyronine was slightly low and thyroid stimulating hormone was above normal. Intravenous injection of thyroid releasing hormone (125 mg) was given and thyroid stimulating hormone was measured. Results at 0 and 70 minutes were 17.5 and 77 μμ/ml respectively. The child is presently being followed up with no treatment.

Discussion

All of our patients had bilateral optic nerve hypoplasia, absence of the septum pellucidum, and various degrees of hypopituitarism. Patients with bilateral optic nerve hypoplasia are initially seen because of suspected poor vision and nystagmus. Most reported cases of optic nerve hypoplasia occur in first-born children[3] as was the case with all of our patients (Table 2).

Definite diagnosis of optic nerve hypoplasia can be made by the appearance of the disk. The disk is small, often one third to one half normal size. By following the choroidal vessels to the disk margin, the size of the disk can be determined. The disk is often surrounded by a flat gray or yellow peripapillary cuff containing granular pigments. In most cases, the size of the peripapillary cuff corresponds to the size of a normal optic disk.[4] There is often a densely pigmented nasal or temporal cresent as well. This appearance is sometimes called a double ring sign.[3] Disk substance is often pale.

TABLE 2

SUMMARY OF CLINICAL FINDINGS*

Findings	Case 1	Case 2	Case 3	Case 4	Case 5
First-born children	+	+	+	+	+
Visual acuity	NLP both eyes	LP both eyes	R.E.: Poor fixation L.E.:3/30 (10/100)	R.E.:6/30 (20/100) L.E.:6/60 (20/200)	NLP both eyes
Pupillary response	Sluggish both eyes	Normal	——	Amaurotic right eye	No reaction in right eye with positive Marcus Gunn sign
Nystagmus	Pendular	Pendular	Pendular	Pendular	Pendular with jerk on left gaze
Ocular deviation	XT	ET	ET	ET	None
Optic nerve hypoplasia	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral
Septum pellucidum	Complete absence	Partial absence	Complete absence	Complete absence	Complete absence
Severe neonatal hypoglycemia with seizures	−	−	−	+	−
Signs of diabetes insipidus	+†	+	+	−	−
Prolonged neonatal jaundice	+	−	−	+	−
Mental retardation	+	+	−	+	−‡
Growth retardation	+	+	+	+	−

*+designates positive; −, negative; NLP, no light perception; LP, light perception; XT, exotropia; and ET, esotropia.
†Fever, dehydration, and polyuria but no polydipsia.
‡Examined at 7 months old only.

Origin of optic nerve hypoplasia is unknown and there is no hereditary pattern recognized. McKinna,[5] however, reported six cases of optic nerve hypoplasia occurring after quinine ingestion taken as an abortive agent after the first missed menstrual period.

The association of optic nerve hypoplasia and absent septum pellucidum has been thoroughly documented.[1,6] Previously septo-optic dysplasia had been diagnosed with pneumoencephalography. Computed axial tomography, a noninvasive technique, may now be used to verify this anatomic malformation.

Finally, we would like to emphasize the association of optic nerve hypoplasia and hypopituitarism, with or without an absent septum pellucidum. The extent of the hypothalamic-pituitary hormonal deficiency can vary from isolated growth hormone deficiency to panhypopituitarism.[7] Children with hypopituitarism can be symptomatic from birth by having severe hypoglycemia and seizures as did our patient in Case 4. Prolonged neonatal jaundice often occurs[7] as it did in two of our cases (Cases 1 and 4). As with other children with growth hormone deficiency, four of our patients were of normal size at birth (Cases 1-4), but failed to grow. Case 5 is unusual in that the patient's growth curve was normal, but he had growth hormone deficiency. Adrenocorticotropic hormone deficiency was present in four of our cases (Cases 1, 2, 4, and 5). Polydipsia and polyuria often with signs of dehydration may become apparent. Three of our cases had diabetes insipidus (Cases 1, 2, and 3), and one of these patients had polyuria without polydipsia (Case 1) (Table 2).

Kaplan, Grumbach, and Hoyt[8] postulated that the hypopituitarism in children with optic nerve hypoplasia might be caused by a diencephalic defect, which results in deficiency of hypothalamic releasing factors and in some cases vasopressin. Autopsy results in a child with septo-optic dysplasia and hypopituitarism described by Patel and associates[7] helped to confirm his hypothesis. The autopsy showed a normal anterior lobe and an absent posterior lobe of the pituitary gland, an anterior hypothalamus consisting of small clusters of primitive cells and foci of heterotopic gray matter and the supraoptic and paraventricular nuclei consisting of cells that were abnormally small and few in number.

The diagnosis of hypopituitarism in children with optic nerve hypoplasia is important because the condition is treatable. Often these children are mentally retarded and their hypopituitarism might be overlooked. Growth hormone is now available. Vasopressin and chlorpropamide, which has a renal effect similar to that of vasopressin, are available for treatment of diabetes insipidus. Thyroid hormone and cortisol are also available if needed.

Summary

Five children had bilateral optic nerve hypoplasia, absent septum pellucidum, and hypopituitarism. Absence of the septum pellucidum was shown by computed axial tomography. All of the children were first-born. One of the children was definitely not mentally retarded and one at age 7 months was developing normally. All of the children had severe visual impairment and nystagmus. Pupillary responses varied. Ocular deviations included one with exotropia and three with esotropia. The extent of pituitary hormone deficiency varied. One child was symptomatic from birth, having severe hypoglycemia and seizures. Two children had prolonged neonatal jaundice. One unusual case had growth hormone deficiency with a normal growth curve. Another child with diabetes insipidus had

dehydration and polyuria without polydipsia.

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INTRAVITREAL AUTOTRANSPLANTATION OF FIBROBLASTS

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Intraocular scar tissue formation is still an uncontrollable complication in the treatment of perforating injuries and retinal detachments. Surgical removal of scar tissue has been attempted[1,2] and some successes have been reported. However, surgical treatment alone seems to be inadequate.

We needed an experimental model to study intraocular scar tissue formation, which would allow quantitation of the ill effects of such a proliferation and permit evaluation of any later therapy. We selected autotransplantation of tissue-cultured fibroblasts into the vitreous cavity as suggested by Algvere and Kock.[3] They observed intraocular strand formation and development of traction detachment. This approach of creating intraocular proliferation is intriguing because the effects of the intraocular scar tissue can be quantitated by the percentage of eyes that develop traction retinal detachments within a given period of time. Finally, this model can be used to evaluate the effect of any therapy reducing intraocular proliferation by simply looking for the number of resulting retinal detachments.[4] We report a refinement and quantitation of Algvere and Kock's[3] original study.

MATERIAL AND METHODS

Tissue culture was obtained from rump skin of pigmented rabbits (2.5 to 3.5 kg) by closely shaving the hair and cleaning the skin with 70% isopropyl alcohol. After local infiltration of lidocaine HCl 1%, a small piece of skin was trephined down to the subcutaneous layer and severed immediately underneath the corium. The piece of tissue was cut into 1-mm^3 sections with scalpels and placed into tissue culture medium (CMRL 1415 with 30% fetal calf serum and two times bicarbonate buffer).[5] The culture was kept in an atmosphere containing 10% CO_2 in air at a temperature of 37°C. After one week, the medium was changed twice weekly (CMRL 1415 with 10% fetal calf serum). Only fibroblasts grew and once a culture became confluent, it was subcultured. The cells were subcultured by washing twice in Dulbecco's phosphate-buffered saline without Ca^{++} and Mg^{++} and then incubated at 37°C for ten minutes with 0.25% trypsin and 0.02% EDTA. The dispersed cells were centrifuged (800 rpm for ten minutes), resuspended, diluted, and recultured. When enough cells were obtained for an experiment, the same dis-

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persion procedure was performed and the centrifuged cells were suspended in a known amount of phosphate-buffered saline (1 to 2 ml). The cell content of a sample was counted and diluted to reach the desired concentration of cells ranging from 10^6 to 10^7 cells/ml. The suspensions were drawn into a tuberculin syringe that was gently agitated to keep cells in suspension.

After harvest, a desired number of fibroblasts were injected into the vitreous cavity of the same rabbit from which they were derived. For this procedure, rabbits were anesthetized with 40 to 50 mg of intravenous sodium pentobarbital. Their pupils had been dilated with 2% cyclopentolate HCl and 10% phenylephrine HCl. Under microscopic control, 0.1 ml of fibroblast cell suspension was slowly injected through a 27-gauge needle that had been passed through the conjunctiva and sclera 5 to 6 mm behind the corneoscleral limbus into the midvitreous cavity. The needle was then withdrawn.

Eyes were examined with a slit lamp and ophthalmoscope, and fundus photographs were taken (before, immediately, one day, three days, seven days, 14 days, and 28 days after the injection). Fluorescein angiograms were taken in selected eyes before and four weeks after injection of cells. To evaluate DNA-synthesis of the injected cells, 50 μCi (0.05 ml) of tritiated thymidine methyl (specific activity, 5.0 Ci/mM) was injected intravitreally two hours before enucleation.

All enucleated eyes were immediately fixed in 5% buffered glutaraldehyde. The corneas were perforated with a trephine to achieve faster and better infiltration of the fixative and to avoid deformation of the eyeball. After 24 hours, the eyes were opened circumferentially 5 mm behind the corneoscleral limbus and the gross specimens were photographed.

For light microscopic evaluation, the specimens were dehydrated in alcohol and embedded in paraffin. Serial sections of selected areas were stained with hematoxylin-eosin, PAS, and Mallory stain. For radioautography, selected sections were coated with Kodak NTB-2 emulsion. After exposure of the coated slides in the presence of a desiccant at 4°C for five days, they were developed with Kodak D19 developer and stained with hematoxylin. Selected specimens were postfixed in 2% phosphate-buffered osmium tetroxide, dehydrated in alcohol, and embedded in Epon; 1.5-μm thick sections for light microscopy were stained with paraphenylenediamine and 0.05-μm thick sections were stained with uranyl acetate and lead citrate for electron microscopic evaluation.

In a first series, the effect of various concentrations of fibroblasts (1 million, one half million, one fourth million, one tenth million) were observed for 28 days in four eyes each. In a second series, one fourth million cells were injected into the vitreous cavity of 71 eyes. Four eyes each were enucleated at various intervals after injection (immediately, one day, three days, seven days, and 14 days). Fifty-three eyes were enucleated after 28 days. Ten eyes served as sham experiments. They were injected with 0.1 ml of phosphate-buffered saline and observed for 28 days.

RESULTS

Clinical observations—In the first series, various amounts of fibroblasts were injected into the vitreous cavity. The more cells were injected, the more intense and longer-lasting was a vitreous haze with appearance of fluffy gray material on the inferior retinal surface. Vitreous strands formed. Higher concentrations of cells caused thicker strands which, when they reached the retinal surface, caused traction retinal detachments, often to such a degree that the retina was torn. However one tenth million cells did not

always show vitreous strand formation and detachments were rare. We selected one fourth million cells for the expanded experiment.

Immediately after injection (71 eyes) of the one fourth million fibroblast suspension, a semitranslucent gray cloud with ill-defined edges was seen in the vitreous cavity. This cloud was always located near the entrance wound, but it did not touch the lens, nor did it reach the retinal surface. Within two hours after the injection, the cloud seemed to have contracted and it had well-defined, rounded edges.

One day after the injection (67 eyes), a well-defined strand could be seen connecting the injection site with the central, now condensed membrane or strand. Some small white clumps adhered to the posterior lens surface in some eyes. The vitreous as a whole looked more hazy. The anterior segment did not show signs of inflammatory reaction.

On the third day (63 eyes) the vitreous haze increased. In some eyes, fluffy white deposits were seen on the inferior retinal surface. The intravitreal strand began to show fingerlike protrusions toward the medullary rays and the optic disk. In 15 eyes, these protrusions had reached the retinal surface in the areas of vascularization, as indicated by slight hyperemia and beginning tortuosity of the finer vessels. (In the rabbit eye the optic nerve head is well above the posterior pole. Extending from it nasally and temporally are two broad white bands of medullated nerve fibers called medullary rays. These are the only vascularized parts of the retina.)

Seven days after transplantation (59 eyes) the vitreous was clear except for the strands. The strands near the entrance site appeared more solid and extended into the midvitreous forming rather thick veils with side branches. These branches usually extended posteriorly and then always into the direction of the vascularized medullary rays or the disk. Twenty-five eyes had strands just touching the medullary ray or the disk. Four eyes showed a definite pucker contracting the vascular tissue over the ray (Fig. 1). In another 15 eyes, traction was exerted on a pucker, resulting in detachment of the medullary ray. In several eyes, branches also extended anteriorly toward the back of the lens.

After 14 days (55 eyes), more thickening of the intravitreal strands was observed. Four eyes showed pucker formation only and 33 eyes showed a combination of puckers and detachments of the medullary rays. In eyes in which a major pucker had developed over the disk, traction was exerted on both sides of the medullary ray resulting in a funnel shaped detachment.

Twenty-eight days after the transplantation, the fundus changes were basically similar to those found after two weeks (Fig. 2). However, the detachments were higher. Out of 51 eyes, three showed

Fig. 1 (Sugita and associates). Where the fibrous vitreous strands connect with the retinal surface, contraction of the surface results (arrow). Usually a retinal detachment begins to develop in this area. (Fundus photograph seven days after injection of fibroblasts into the rabbit vitreous cavity.)

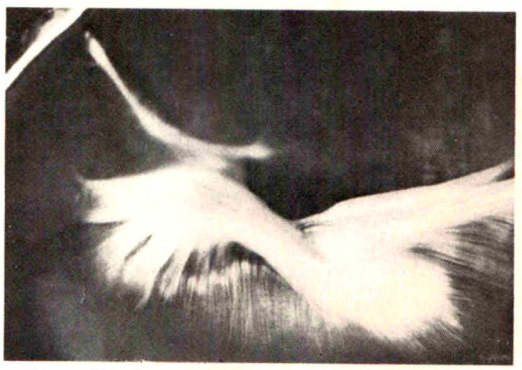

Fig. 2 (Sugita and associates). Thick fibrous vitreous strand connects with the disk and medullary rays causing a high retinal detachment (photograph of fixed pathology specimen four weeks after intravitreal fibroblast injection).

pucker formation only and 29 eyes showed a combination of puckers with traction detachment. Some eyes exhibited definite neovascularization.[6] All sham eyes showed no pathologic changes during the four-week period.

Histology, electron microscopy, and radioautography—Fibroblasts taken from tissue culture and examined immediately after isolation or immediately after injection in the vitreous cavity, had a similar appearance. They accumulated in clusters in the vitreous cavity. The cells had a round shape with a prominent nucleus. Fine short cytoplasmic protrusions appeared as villi or irregularly shaped pseudopods. The cytoplasm contained an abundance of mitochondria but few microfilaments. Signs of high cellular activity such as dilated rough endoplasmic reticulum, were seen in only a few cells (Fig. 3). Other cells were disintegrating and only cellular debris was recognized. No labelled fibroblasts were found in the vitreous.

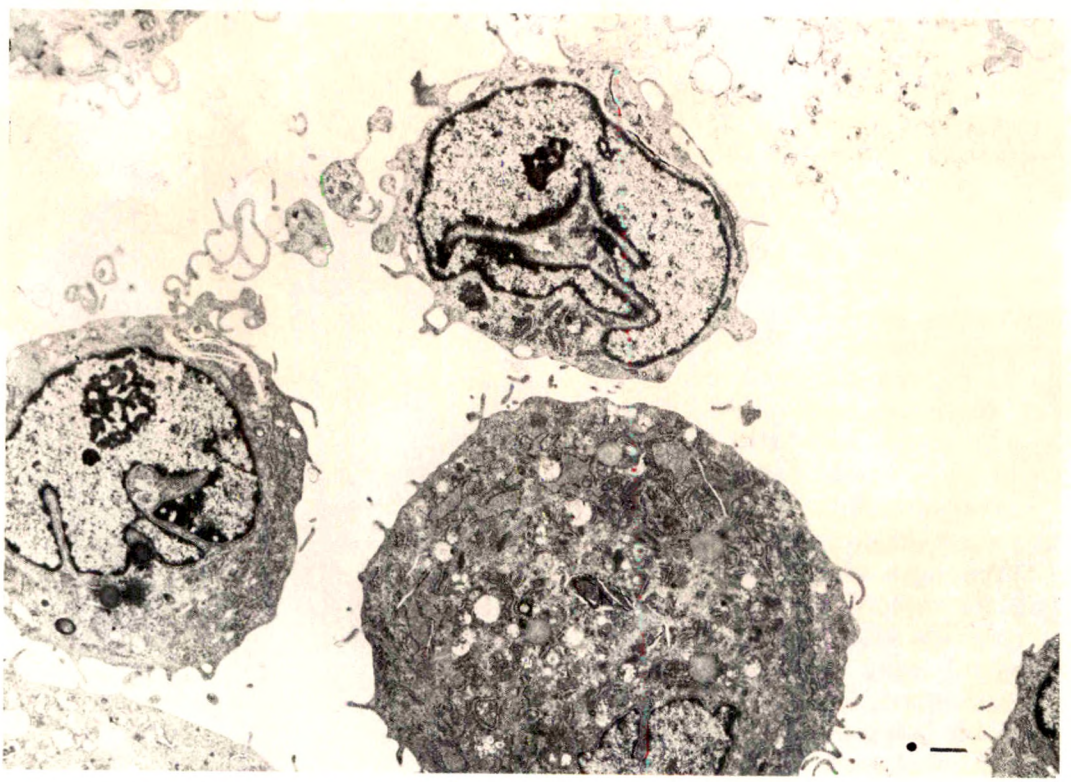

Fig. 3 (Sugita and associates). Freshly injected fibroblasts are round and isolated from each other (×4,900, bar gauge = 1 μm).

One day after transplantation, blood-born cells such as polymorphonuclear leukocytes were found preretinally and intermixed with fibroblasts of various shapes and stages of vitality. Cell debris was prominent. Some elongated fibroblasts that appeared either isolated or in bundles were distinct. They showed dilated rough endoplasmic reticulum and large amounts of microfilaments with a suggestion of dense bodies near the cell membrane and a more irregular network of slightly thicker filaments elsewhere in the cell. No radioactive labelling was seen at this stage.

After three days, definite intravitreal strand formation was found. Elongated cells surrounded clusters of a mixture of cell debris, round fibroblasts, a few inflammatory cells, and macrophages. Other strands consisted solely of elongated cells with spindle-shaped nuclei (Fig. 4, left). Some fibroblasts had settled on the surface of the medullary ray forming a single or multiple cell layer with the underlying superficial tissue thrown into folds. Still intermixed were round fibroblasts. Electron microscopically, several of the elongated cells had the features of developing myofibroblasts, with prominent microfilament content, dense bodies, cell junctions, and a convoluted nucleus (Fig. 4, right). Radioautography revealed some labelling of fibroblasts.

Seven days after transplantation, lymphocytes accumulated near the intravitreal strand, over the retinal surface, and surrounded superficial retinal vessels. Solid masses of fibrous tissue were overlying the retina in the area of the medullary ray or disk. This tissue pulled the retina heavily into folds and detached it often with necrosis of the outer retinal layer. Cells on the outside of this fibrous mass were usually elongated with oval nuclei, forming what looked like a fibrous capsule (Fig. 5). The inside of the mass consisted of more irregularly oriented cells. Fingerlike protrusions of the fibrous tissue usually had the cells oriented along their axes. Mallory stain showed intense blue staining, indicating a high collagen content. Many thin-walled endothelium-lined vessels of small but also large caliber were found in this tissue. They contained blood cells. Radioautography showed a large number of labelled cells. Most of these cells were on the outside layers of the strand in the area of immediate retinal contact (Fig. 6). In the immediate vicinity of the retina, it was difficult to differentiate between DNA synthesizing injected fibroblasts and possible proliferation from the retinal vessels. Intravitreal parts of the strand looked different. They contained large numbers of necrotic cells that were surrounded by a thin layer of viable fibroblasts, some of which were radioactively labelled. These parts of the strands always lacked new vessels.

After 14 days, the findings were similar to those after seven days. The fibrous tissue became denser and elongated cells were more oriented along the axis of the strand. Many cells contained myofilaments with dense bodies and had a convoluted nucleus (Fig. 7). The rough endoplasmic reticulum was widely dilated. The number of radioactively labelled cells was reduced compared to the findings at one week; however, there were still clear signs of thymidine incorporation.

By four weeks, leukocytes and lymphocytes had disappeared. The fibrous tissue in the vitreous and on the retina showed widely spaced, elongated cells embedded in a matrix of collagen. The cells themselves had a widely dilated endoplasmic reticulum and contained densely packed microfilaments. The vitreal parts of the fibrous strands were avascular. The center of the strands contained irregularly shaped cells filled with large, homogeneous, electron dense, usually round

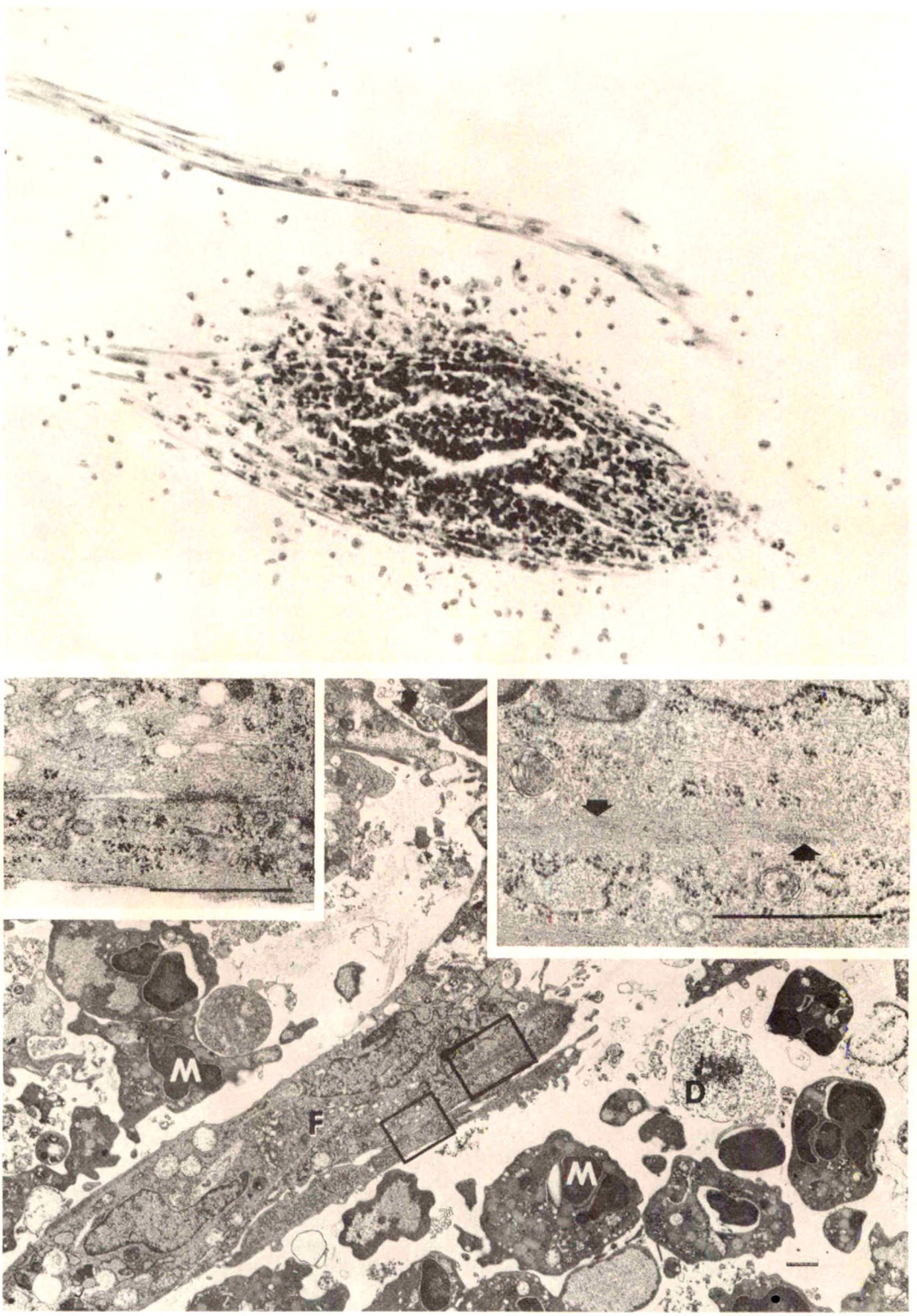

Fig. 4 (Sugita and associates). Top, Three days after fibroblast injection, cells are aligned into strands. Cells on the inside of thick strands are often necrotic (×580). Bottom, Electron micrograph shows elongated fibroblasts (F) among macrophages (M) and cell debris (D). The fibroblast shows microfilaments with developing dense bodies (right inset, arrows), has a convoluted nucleus and cell junctions (left inset) suggesting a myofibroblast (×4,400, left inset ×22,000; right inset ×25,800, bar gauge = 1 μm).

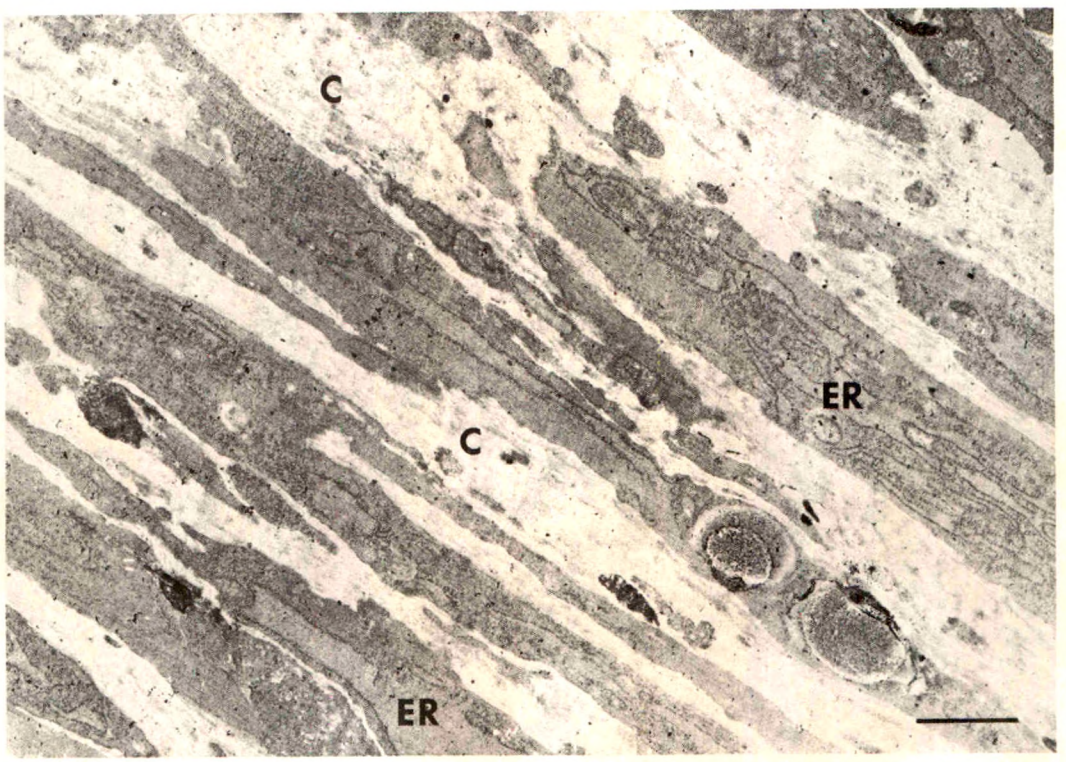

Fig. 5 (Sugita and associates). Densely packed stretched fibroblasts with widely dilated rough endoplasmic reticulum (ER) surrounded by collagen containing matrix (C) seven days after fibroblast injection (×13,200, bar gauge = 1 μm).

granules. The parts of the strands that were in contact with the retina showed heavy vascularization in the stroma with irregularly oriented and rounded cells.

Discussion

In Algvere and Kock's[3] original experiment one million tissue cultured skin fibroblasts were autotransplanted into the vitreous cavity. We found that in their model a severe intraocular inflammation occurred that lasted clinically for at least two weeks. Strand formation was intense and the resulting traction detachments were difficult to evaluate because large holes were torn into the retina and often all of the retina was pulled into one big scar tissue mass behind the lens. Finally, it required a lot of tissue-culture time to be able to harvest one million cells for each eye.

We found that one fourth million cells were more adequate for our purposes. The clinically visible inflammatory reaction in the vitreous cavity lasted less than one week. Vitreous strands developed and extended toward the retina. Early changes at the retinal level consisted of pucker formation on the medullary rays or optic nerve head. This became visible as vessels were dragged where the vitreous strand touched the surface of the retina. Later elevation of this area with definite traction retinal detachment developing was observed. Pucker formation occurred as early as three days after injection of fibroblasts; traction detachment occurred as early as seven days after injection. By the end of four weeks, 29 of 53 eyes (55%) had a combination of preretinal pucker and traction detachment, whereas another three eyes (6%) showed a pucker forma-

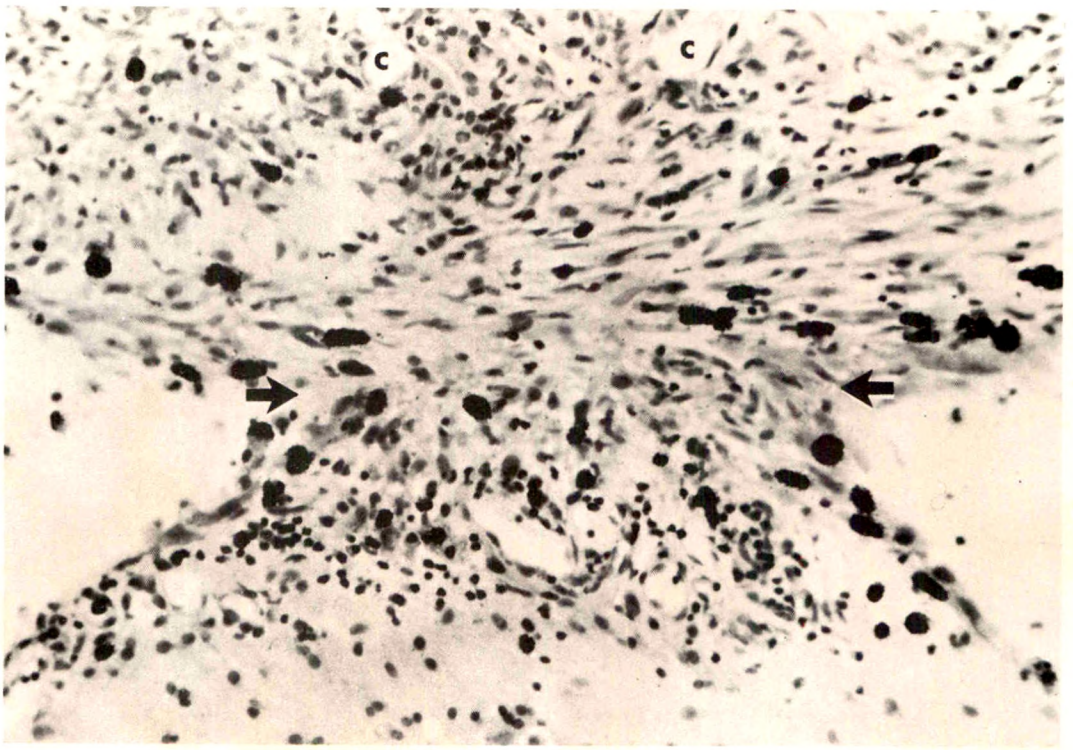

Fig. 6 (Sugita and associates). Arrows separate vascularized part of retina from overlying accumulation of fibrous tissue. There is no sharp boundary between the two tissues. Marked labelling after tritiated thymidine methyl injection (labelled cells) indicates heavy proliferation. New capillaries (C) are visible in the fibrous tissue (×660).

tion only. The detachments were localized and without retinal holes.

When the fibroblast suspension was injected into the vitreous cavity, varying amounts of cells were either dead or so damaged that they died within a short period of time. This explains the cell debris and the accumulation of macrophages and leukocytes in the early stages after injection. Surviving cells, which had been made round-shaped during isolation for injection purposes (Fig. 3), quickly regained their original spindle shape. The amazingly quick directional orientation of most of these cells was histologically proven after three days. Because the strand formed along the injection tract, it was assumed that the cells oriented themselves along condensed vitreous fibrils.

Why the cells become more and more compacted is not understood. The initial cloud of injected material contracted visibly two hours after injection and after three days definite histologically proven strands were seen. Presumably, the cells attract each other. Appearance of new cells by proliferation could not be the main factor because proliferation occurred later and not in the center of the strand, but rather in its periphery.

Within the vitreous cavity proliferation was fairly low and then only on the outside of the fibrous strand. The more the strands approached the retina, specifically the vicinity of the optic nerve head and the medullary rays, the more intense the proliferation became. It is not always possible to separate fibrous proliferation

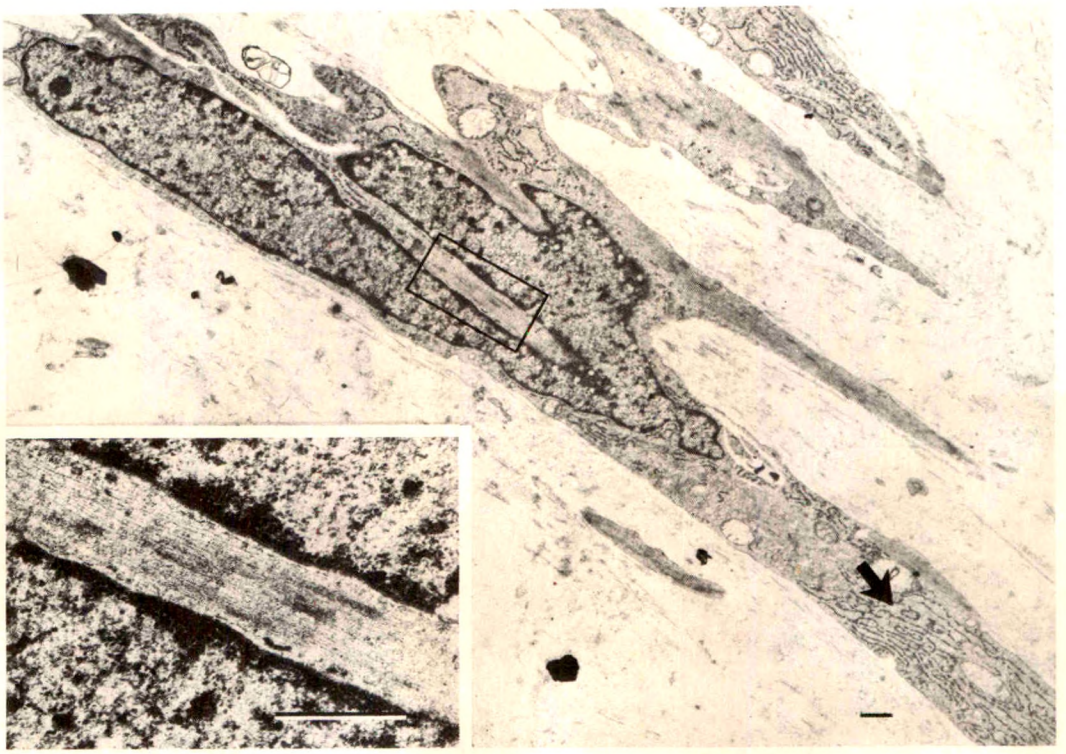

Fig. 7 (Sugita and associates). Mature myofibroblast 14 days after injection. Note the convoluted nucleus and the many dense bodies and microfilaments (inset). The rough endoplasmic reticulum is dilated (arrow) (×4,300; inset, ×17,300; bar gauge = 1 μm).

from vascular proliferation. Our findings suggest that a factor that ultimately stimulates multiplication of the cells is more available in the vicinity of the optic nerve head and medullary rays than in the vitreous cavity, and nearly unavailable within the vitreous strands.This factor may simply be more adequate nourishment of the cells in the vicinity of the retinal vessels, or a factor produced by the fibroblasts that stimulates vascular proliferation, or both.

Intracellular microfilaments may be the anatomic correlate for the contraction of the cells[7] in the strands, causing pucker formation as early as three days after the injection of the cells. Whereas isolated, rounded fibroblasts immediately after injection show few filaments; these increase quickly and are abundant by the first day within the cells and remain visible. Dense bodies, convoluted nuclei, and cell junctions appear and suggest formation of myofibroblasts. Basal lamina formation is said also to occur occasionally in myofibroblasts,[8] but this did not occur in our specimens. Myofibroblasts have been shown to appear during wound healing.[7] Contraction of the cells remains clinically irrelevant as long as the cells grow within the vitreous. The strand simply condenses more when it contracts. However, when the cells have attached to the retina and grow along its surface, contraction will result in distortion of the retinal vessels. The forces increase with the increasing number of cells near the retina and the pucker becomes more visible. Simultaneously, the contraction along the vitreous strand continues, resulting final-

ly in detachment of the retina. These findings bear great similarity to what seems to occur in perforating eye injuries.[9] There is also a great resemblance to events that occur during the development of massive periretinal proliferation where cells deriving from pigment epithelium turn into fibroblastlike cells and form membranes and strands that exert traction on the retina.[10,11]

Since preretinal puckers and traction detachments resulting from intravitreal injection of fibroblasts can be quantitated easily, we think that this is an experimental model that can be used to evaluate the effect of any therapy that prevents intraocular proliferation of fibroblasts. Instead of having to quantitate the number of fibroblasts, the number of developing traction detachments can be used as a factor of fibroblast growth. In the following study we delineate the effect of intraocular injection of corticosteroids on this system.[4]

Summary

Tissue cultured skin fibroblasts autotransplanted into the vitreous cavity of rabbit eyes formed intravitreal strands that grew toward the medullary ray and optic nerve head and caused preretinal puckers and traction detachment. After four weeks, 32 of 51 eyes (63%) developed these changes.

Light and electron microscopy revealed initial cell death. Remaining cells aligned themselves quickly into strands and began to multiply as shown by tritiated thymidine methyl incorporation. The appearance of cells that resemble myofibroblasts may explain the contractability of the strand.

Because the effect of intraocular proliferation can be quantitated by the number of puckers and retinal detachments developing, this model may be useful for the study of therapeutic means to reduce intraocular proliferation.

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INHIBITION OF INTRAOCULAR PROLIFERATIONS WITH INTRAVITREAL CORTICOSTERIODS

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The techniques provided by vitreous surgery[1] have made it possible to attack fibrous proliferation inside the eye as it is found after injuries and in massive peri-retinal proliferation.[2] The most serious complication is the formation of new fibrous tissue a few weeks after successful removal of intraocular scar tissue. Simple surgical removal of scar tissue is inadequate[2] and some means must be found to prevent the formation of new intraocular tissue.

A reasonable approach to this problem would be to inhibit reproliferation of the tissues that remain in the eye after surgery. In looking for an appropriate drug we selected a corticosteroid because many of the effects of corticosteroids on fibroblasts are known.[3,4] We chose dexamethasone because this drug has a strong inhibitory effect on proliferation and has been used intraocularly.[5]

A method to simply and indirectly quantitate intraocular proliferation is the development of traction retinal detachment after injection of tissue cultured fibroblasts into the vitreous cavity.[6] Any reduction of strand formation results in fewer retinal detachments. Thus the effect of a proliferation-reducing drug can be measured by the decrease in the number of retinal detachments.

MATERIAL AND METHODS

The technique for obtaining a tissue culture of fibroblasts from rabbit rump skin and the autotransplantation of one fourth million of these cultured cells into the vitreous cavity has been described in detail in the previous article.[6] Immediately following the injection of the fibroblasts into both eyes (done with a 27-gauge needle inferotemporally), 24 rabbits received an additional intravitreal injection of 1 mg of dexamethasone alcohol suspended in 0.1 ml of physiologic saline solution into each eye. This injection was also done with a 27-gauge needle but from a separate site 5 to 6 mm posterior to the corneoscleral limbus superotemporally and was directed at the midvitreous cavity. To avoid direct and systemic effects of the injected corticosteroid, fellow eyes were not used as controls. Instead 24 rabbits received 0.1 ml of Dulbecco's phosphate-buffered saline solution into both eyes as their second injection.

All animals were observed before and

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immediately after (one, three, seven, 14, and 28 days) the injection by slit lamp and ophthalmoscope. Each time, fundus photographs were taken. The animals were then killed by an intravenous overdose of sodium pentobarbital. The globes were enucleated immediately and placed in cold, phosphate-buffered 5% glutaraldehyde. A corneal button was removed to allow better infiltration of the fixative. After a minimum fixation time of 24 hours the eyes were rinsed in phosphate-buffer solution and bisected circumferentially 4.5 mm posterior to the corneoscleral limbus. The calottes were examined under the dissecting microscope and photographs were taken. The clinical and gross pathologic findings were evaluated by each of us independently.

The number of detachments and clinically visible neovascularizations that had developed were counted in the eyes of each group. The findings were analyzed with the chi-square and the Fisher's test. Three eyes were excluded from this series because they had mechanical retinal damage (two eyes from the treated group and one eye from the untreated group).

RESULTS

The rabbit has relatively little vitreous gel (approximately 1.5 ml). Therefore, the injection of 0.1 ml twice into the eye increases the intraocular pressure temporarily as indicated by a small shift of the intravitreal clouds of cells and corticosteroids toward the entrance site and a small loss of vitreous from the scleral perforation when the needles are retracted. This loss was minimized by slow injection and by leaving the needle in place for a time after injection.

Immediately after injection and at any time later during the observation, the two materials injected into the vitreous cavity could always be separated (Fig. 1). The corticosteroid formed a dense, brightly white, well-rounded cloud, whereas the cells were initially more yellow and diffuse. Within two hours the cell suspension condensed to a strandlike pattern or appeared in more isolated clumps.

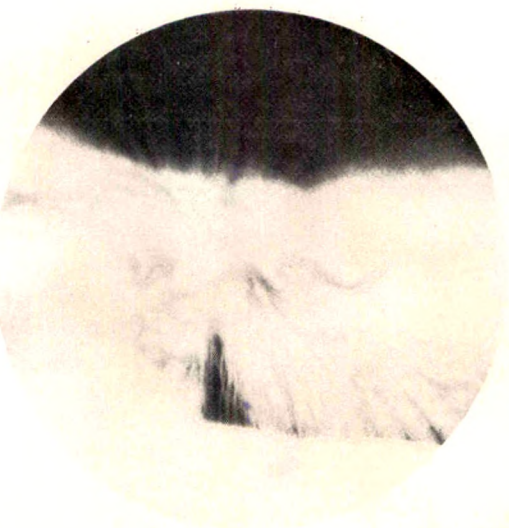

Fig. 1 (Tano and associates). Rabbit eye after injection of fibroblast suspension (seen as gray cloud over disk) and dexamethasone alcohol (white cloud inferior to disk).

After one day the injected cells formed a well-defined strand. It was usually connected to the site of the injection. No difference between the two groups was noted, except that an accumulation of fluffy material preretinally (representing cell debris and inflammatory cells[6]) in the inferior vitreous cavity was markedly less in the corticosteroid treated eye.

By three days in many of the untreated eyes, the intravitreal strands had taken a direction toward the vascularized part of the retina and attached to the disk or medullary ray (13 of 47 eyes, 28%). Hyperemia developed around this attachment and tortuosity of the finer vessels was seen in this area giving the appearance of a preretinal pucker. Some puckers appeared without a visible connection to

the intravitreal strands and sometimes more than one pucker developed. There was also one traction detachment (2%). In the treated eyes the attachment of the intravitreal strand to the retina occurred in only two of 46 eyes (4%). One detachment was found (2%). The corticosteroid clouds were slightly reduced in size.

By the seventh day, 14 of 47 eyes (30%) showed traction on the retina. In treated eyes the strands were much less frequently connected to the retina and traction detachments were found in four of 46 eyes (9%).

On the 14th day, the vitreous strands in the untreated eyes were more conspicuous than earlier, and the number of retinal detachments (25 of 47 eyes, 53%) was higher than in the treated group (eight of 46 eyes, 17%). Also the heights of the detachments were much less pronounced in the treated group than in the untreated group. The corticosteroid had disappeared from many eyes. Only a few eyes showed a small white dense remnant in the inferior vitreous cavity.

By 28 days, the untreated group showed traction detachments in 27 of 47 eyes (57%) (Fig. 2). The detachments usually had increased in height, as compared with the 14th day. The treated group, however, had only 11 of 46 eyes (24%) with traction detachment. No corticosteroid could be detected in any of the eyes (Fig. 3).

Neovascularization occurred in some eyes. These were clinically visible as fine vascular loops growing into the clear vitreous at the base of the vitreous strand where they were in contact with the disk or medullary ray (Fig. 4). A detailed description of this phenomenon appears elsewhere.[7] The neovascularization was found in nine of 47 eyes of the untreated group (19%) but only in two of the 46 treated eyes (4%) (Fig. 5).

Statistical evaluation of the differences between the untreated group and the treated group showed that they were significant starting at the seventh day (Fig. 5).

Fig. 2 (Tano and associates). High elevation of medullary ray caused by traction of fibrous vitreous strand.

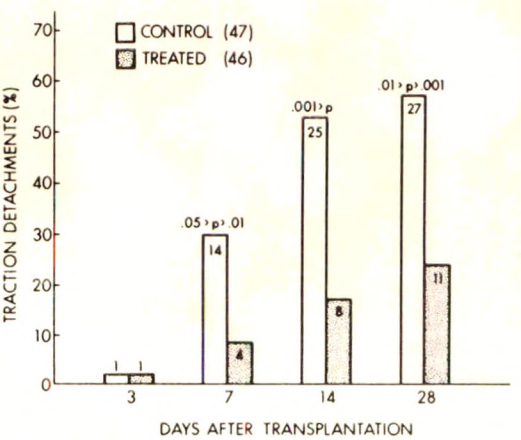

Fig. 3 (Tano and associates). Graph showing the number of developing traction detachments after intravitreal fibroblast injection without (control) and with additional corticosteroid injection (treated). The statistical significance of the difference is noted above the bars.

Fig. 4 (Tano and associates). Retinal neovascularization can occur where vitreous fibrous strands attach to the medullary wing or disk. A fan of new vessels is visible.

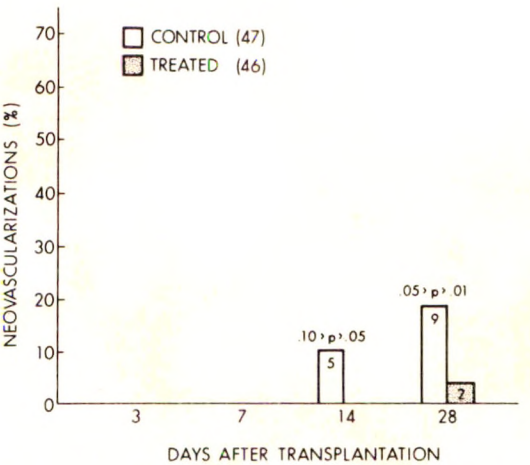

Fig. 5 (Tano and associates) Graph showing the number of eyes in which retinal neovascularization occurs after intravitreal fibroblast injection without (control) and with additional corticosteroid injection (treated). The statistical significance of the difference is noted above the bars.

Discussion

The results are significant enough to indicate that dexamethasone alcohol reduces the development of retinal detachments when injected intravitreally together with cultured fibroblast cells. Detachments are dependent on the development of intravitreal fibrous strands. These strands normally grow from the midvitreous cavity toward the vascularized parts of the retina, contact the retinal surface to form puckers, and pull on the retina causing retinal detachments in a high percentage of cases. Because it is difficult to quantitate the actual proliferation, we have used the development of retinal detachment as an indirect factor of this proliferation. Indeed, with dexamethasone alcohol, many strands remain thin and do not reach the retina and when this does occur, detachments are less frequent and less prominent.

Corticosteroids have an inhibitory effect on the growth of fibroblasts.[3,4,8–10] Inhibition, however, occurs only with high levels of corticosteroids,[11] much higher than one would achieve with topical, parabulbar, or systemic applications. There may also be a selective damage to fibroblasts by high doses of corticosteroids.[12] To achieve these levels and to avoid as many systemic side effects as possible, we selected an intravitreal application.

Dexamethasone alcohol was selected as a high potency corticosteroid for inhibition of fibroblast growth, which is actually 75 times that of corticosterone.[3] The commonly used water soluble dexamethasone phosphate seems inadequate because it has a half-life of only three hours when injected into the vitreous cavity.[5] Dexamethasone alcohol, however, is a corticosteroid that is much less water soluble and therefore disappears visibly from the rabbit vitreous cavity between seven and 14 days.

Previous experiments have shown the proliferative activity of intravitreally injected fibroblasts to be highest around

seven days after injection.[6] Therefore, we looked for a corticosteroid that would be available in adequate concentrations for at least that long and still be soluble enough to provide a high concentration. We selected a relatively high corticosteroid dose. Wheeras normally the therapeutic dose of dexamethasone is in the maximum range of 1 mg/75 kg of body weight, the intraocular dose corresponds to 1 mg/3 g of eye weight. However, the protracted dissolution of the drug reduces this value considerably.

The inhibitory effect of the corticosteroids could also be observed on the development of retinal neovascularization. This neovascularization occurs whenever fibrous tissue comes into contact with the retinal vascularization of the rabbit eye. Presumably the neovascularization is stimulated by the fibrous tissue itself.[7] A reduction in fibroblast growth, as it was shown in our experiment, should in itself cause a reduction of vascular growth. The corticosteroid probably has an additional direct inhibitory effect on the proliferation of vascular tissue.[13]

Our experiment covers only a four-week time span. Once the corticosteroid has disappeared from the eye its inhibition of fibroblast growth may terminate as well. This can be concluded from the reversibility of inhibition of cultured fibroblasts after removal of the corticosteroid.[4] Possibly, once the initial inhibition effect wears off, proliferation will be resumed and the final result would be the same in the treated as well as in the untreated group. Long-term observations after dexamethasone alcohol injection are needed. Higher concentrations of corticosteroids might yield better results. Finally, a study should be done on the length of time corticosteroids should be available within the eye to inhibit fibroblast growth permanently.

There are several acute proliferative diseases that might respond to high doses of intravitreally injected corticosteroids. Heavy proliferation of fibroblastlike cells occurs in massive periretinal proliferation[14,15] and also after injury of the eye. If it can be shown that selected corticosteroids in high doses are not toxic to the eye, this therapeutic avenue should be further explored. Because neovascularization was also suppressed, we speculate that neovascularization as it acutely occurs in rubeosis iridis might be amenable to such a corticosteroid therapy.

Summary

Autotransplantation of one fourth million tissue cultured fibroblasts from rabbit rump skin into the vitreous cavity resulted in intravitreal strand formation and traction retinal detachment (27 of 47 eyes, 57%). A single intravitreal injection of 1 mg of dexamethasone alcohol inhibited fibroblast growth as judged by the significantly reduced number of retinal detachments (11 of 46 eyes, 24%).

Retinal neovascularization that was observed when fibrous strands came into contact with vascularized retina (nine of 47 eyes, 19%) was also inhibited after corticosteroid application (two of 46 eyes, 4%).

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NOTES, CASES AND INSTRUMENTS

LIMITED SUPERFICIAL DEBRIDEMENT TO IMPROVE CORNEAL CLARITY DURING CLOSED VITRECTOMY

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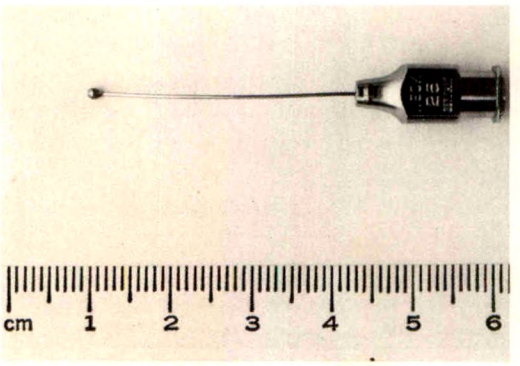

Fig. 1 (Spencer, Newsome, and Schepens). Olive-tipped irrigator.

Successful vitreoretinal surgery requires clarity of the anterior ocular media. Except with open-sky techniques, the surgeon must view the procedure through the cornea. Corneal epithelial edema developing during operations is often a major technical problem.

Despite routine irrigation, epithelial edema is common during operations on diseased corneas and corneas insulted by manipulation or chemical exposure.[1] Many surgeons remove the entire epithelium at the first loss of clarity. Although this procedure is effective and usually free of sequelae, it does constitute an additional manipulation and can be complicated by persistent epithelial defects, ulcers, and recurrent erosion. These problems are especially common in diabetics,[2] who make up a large percentage of vitrectomy patients.

Using the sew-on contact lens for closed vitrectomy, we have observed development of corneal clouding even when a viscous hyaluronic acid coating solution has been applied to the cornea.[3] This cloudiness can be cleared by gentle sweeping of an olive-tip irrigator over the epithelial surface (Figs. 1 and 2) with or without removal of the contact lens. Clearing of the cornea by this method is accompanied by debridement of the most

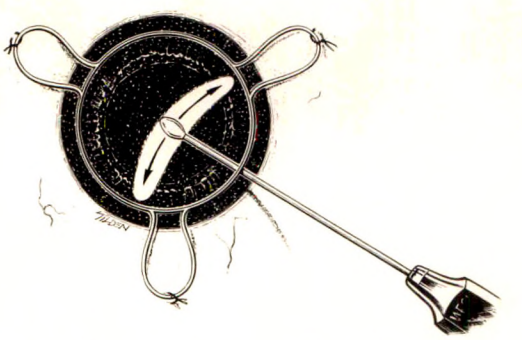

Fig. 2 (Spencer, Newsome, and Schepens). Technique of superficial debridement with olive-tipped irrigator.

From the Eye Research Institute of Retina Foundation and Retina Associates, Boston Massachusetts (Drs. Spencer and Schepens), and the National Eye Institute, Bethesda, Maryland (Dr. Newsome). This study was supported by grants from the Massachusetts Lions Eye Research Fund, Inc., and from Research to Prevent Blindness, Inc. (Dr. Schepens).

Reprint requests to Librarian, Eye Research Institute of Retina Foundation, 20 Staniford St., Boston, MA 02114.

superficial layer of epithelial cells visible through the operating microscope. Because many of these cells are ready to be desquamated, debridement is easy. Debrided cells were seen by light microscopy of a Giemsa-stained preparation aspirated from the corneal surface after a clearing sweep during a closed vitrectomy (Fig. 3).

In contrast with the technique of rolling the cornea with a dry swab,[4] this clearing procedure depends on debridement for its effectiveness. It has the advantage of requiring only a light sweeping touch, and so it is atraumatic and can be used repeatedly. The regenerative basal layers of the epithelium usually need not be disturbed.

Edema may frequently occur even in healthy corneas during closed vitrectomy because of hypoxia. As with any type of contact lens, oxygenation of the corneal epithelium depends on the circulation of an oxygenating medium behind the lens; that is, tears, isotonic saline, or other operative irrigating solutions. It has been our clinical impression from its use in more than 80 cases that a viscous hyaluronic acid solution offers superior preservation of corneal clarity in vitreoretinal surgery.[5] However, even when it is used in combination with a contact lens, the superficial wing cells of the corneal epithelium are likely to be subjected to lowered oxygen tension. Development of an optical system compatible with the operating microscope that could provide an image of the vitreous cavity without the use of a contact lens would be desirable.

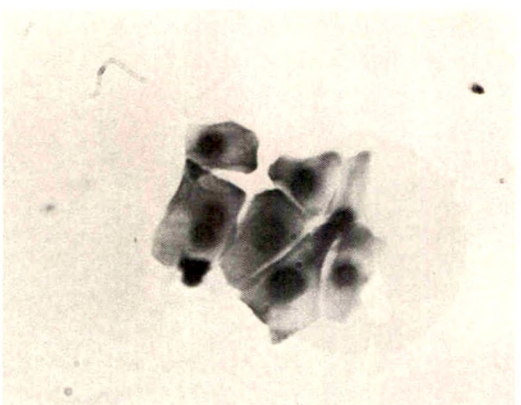

Fig. 3 (Spencer, Newsome, and Schepens). Cells swept from corneal surface during closed vitrectomy, exhibiting characteristic flattened, squamous morphology of superficial corneal wing cells (Giemsa, ×240).

Summary

We controlled the development of epithelial edema of the cornea during closed vitreoretinal surgery even when the technique required continuous use of a contact lens by gentle debridement of only the shaggy, edematous superficial layer of wing cells, using an olive-tip irrigator. This technique may avoid the necessity of completely removing the epithelium and the attendant postoperative complications.

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MYCOBACTERIUM CHELONEI AND ORBITAL GRANULOMA AFTER TEAR DUCT PROBING

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Mycobacteria of the fortuitum complex are uncommon ocular pathogens. These organisms may involve the eye as an infrequent cause of indolent corneal ulceration after trauma or keratoplasty.[1–7]

We describe a case that shows orbital granuloma caused by *Mycobacterium chelonei* (subspecies *abscessus*) after lacrimal duct probing. To the best of our knowledge, this is the first case report of orbital involvement with this organism after instrumentation of the lacrimal system. We also describe the role of the *M. fortuitum* complex in ocular disease and the problems in establishing this diagnosis.

CASE REPORT

A 75-year-old woman had chronic asthma and a ten-year history of chronic epiphora, greater in the right eye than in the left eye. She had been taking systemic prednisone in 20-mg doses daily for several years. On Sept. 30, 1975, she underwent an uncomplicated dacryocystorhinostomy on the right eye under general anesthesia. At this time, the left tear duct was probed under sterile conditions and the probe was passed into the nose. No false passages were noted at that time. Her postoperative course was uneventful until Oct. 22, 1975, when she complained of a lump in the left lower eyelid. A small lump was present in the area of the left lacrimal fossa, which was presumed to be a dilated sac. Minimal epiphora was present and the duct was successfully irrigated with saline but not probed. During the next two weeks, the lesion enlarged and could be palpated as a pea-sized lump in the area of the lacrimal sac connected with firm ribbonlike mass between the globe and the interior orbital rim extending to the lateral aspect of the orbit. No proptosis, diplopia, pupillary abnormality, or decreased vision were noted. Results of orbital x-ray films were normal. Her medical history revealed that she had undergone a radical mastectomy for carcinoma in February 1975 and that she was taking 20 mg of prednisone daily for asthma. We believed that the lesion was most likely metastatic breast carcinoma and a biopsy specimen was taken with the patient under local anesthesia on Dec. 9, 1975 (Figs. 1 and 2). A 10-mm incision was made in the midportion of the eyelid below the tarsus. At the level of the orbital septum, a firm, white, rubbery mass was encountered. This mass seemed to be infiltrating orbicularis muscle, orbital septum, and fat. The original pathology report described chronic granulatous inflammation with giant cells and was

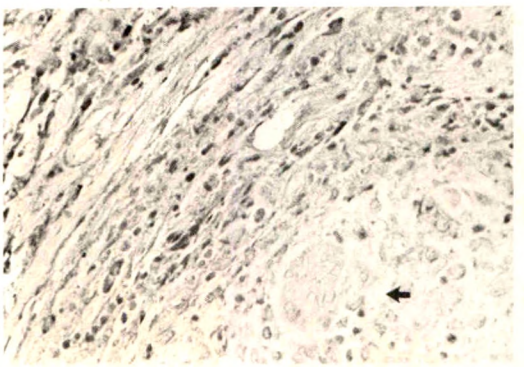

Fig. 1 (Smith and asociates). Biopsy specimen reveals round cell infiltration and areas of multinucleated giant cells characteristic of granulomatous inflammation (arrow) (hematoxylin and eosin, ×60).

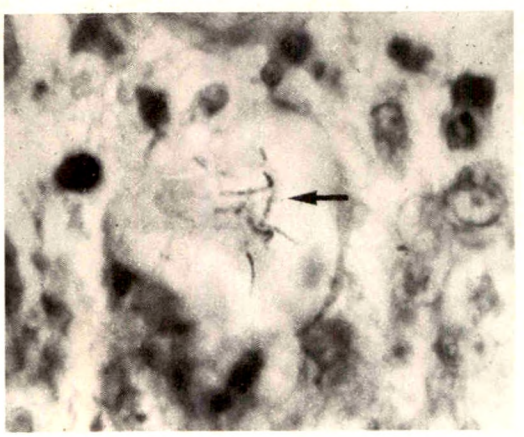

Fig. 2 (Smith and associates). High-powered view reveals acid-fast organisms in areas of granulomatous inflammation (arrow) (Kenyon acid-fast stain, ×850).

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believed to be most consistent with a chalazion. The pathologist was contacted and was assured that the lesion was not from the tarsus but from the orbit. Special stains, including acid-fast, were then performed that showed acid-fast organism. Subsequently, the patient was admitted here on Jan. 16, 1976. Chest x-ray films and skin tests for tuberculosis were negative. With the patient under local anesthesia, an incision was made 4 mm beneath the eyelash line along the entire length of the left lower eyelid; the white fibrous mass extended from the area of the lacrimal sac to the lateral orbital rim between the globe and the inferior orbital rim. Because the lesion adhered to the deeper orbital structures, no attempt was made to excise it completely. Most of the lesion was excised within the specimen measuring 20 × 4 mm. Specimens were sent for pathologic examination, routine culture and susceptibility tests, and for acid-fast smears and culture. Routine cultures were negative for bacteria and fungi. *Mycobacterium chelonei* (subspecies *abscessus*) was isolated. It was resistant to most of the antituberculous drugs. Testing to the common antibacterial agents revealed susceptibility only to kanamycin, with slight susceptibility to erythromycin. Because of the toxic nature of kanamycin and because it can only be given by injection, the patient was given erythromycin for three months. The lesion gradually resolved. An attempt by her internist to taper the prednisone resulted in a severe exacerbation of her asthma necessitating re-institution of the cortisone. Presently, the patient has had a three-year follow-up; no palpable lesion is evident and only a small scar from the surgery remains. Visual acuity in the left eye remains at 6/9 (20/30), with normal results of ophthalmoscopic examination, full visual fields, and normal extraocular motility. Hertel exophthalmometry readings are equal.

Discussion

The *M. fortuitum* complex of atypical acid-fast organisms is widely distributed in soil and water. Runyan[8] proposed a classification of acid-fast organisms in 1959 and described four groups based on colony pigmentation after exposure to light or darkness, and growth rate on artificial media. The *M. fortuitum* complex is nonpigmented, forms mature colonies in less than seven days, and belongs to Runyon's Group 4. The species of mycobacteria within the *M. fortuitum* complex are *M. fortuitum, M. chelonei* subspecies *abscessus,* and *M. chelonei* subspecies *chelonei.* The taxonomy of this complex has undergone a number of changes, and its members are frequently identified incompletely, leading to the almost synonymous use in published reports of *M. fortuitum, M. abscessus, M. ranae, M. chelonei,* and *M. borstelense.*

Ocular involvement with the *M. fortuitum* complex has generally been limited to a chronic indolent form of keratitis that is resistant to therapy and may require surgical intervention. Turner, and Turner and Stinson,[1,2] Kirber, Kirber, and Dubin,[9] Lazar, and associates,[10] Levine,[11] Sexton,[12] and Willis and Laibson[3] have described patients with such corneal involvement. Several have been patients undergoing penetrating keratoplasty.

The present case is the first report, to the best of our knowledge, of orbital involvement with *M. chelonei* subspecies *abscessus* although Levine[11] reported a case of bilateral orbital involvement with the avium-intracellulare complex of atypical *Mycobacterium.* In Levine's case, a young boy was originally thought to have atypical Hand-Schüller-Christian disease, and had been treated for four years with prednisone. In addition to bilateral orbital infection with atypical acid-fast bacteria, he had multiple scalp abscesses.

The present case seems to have followed probing of the lacrimal system that was performed with the patient under general anesthesia and under sterile conditions. It is unclear as to how the infection was introduced beneath the skin, although the patient certainly had the predisposing factors of systemic prednisone and asthma, which may have played a role in the cause of this process. Possibly the organism was harbored in the tear sac and was introduced subcutaneously during the tear duct probing. However, the other orbit did not develop a mycobacterial abscess after dacryocystorhinostomy.

Mycobacterium fortuitum abscesses after subcutaneous injections are well known. Vendepette, Desmyter, and Gatti[13] reported 100 subcutaneous ab-

scesses and Owens, Smith, and Coultras[14] reported 50 similar injection site abscesses. A tear duct probing is a form of injection although, at the time of probing, there was no note that the mucous membrane of the duct had been disturbed or that any false passage into the subcutaneous tissues had been made. Indeed, the tear duct seemed to irrigate freely.

The difficulty in establishing a diagnosis of ocular mycobacterial disease is shown by the present case. Only the use of acid-fast stain and consultation with the pathologist allowed the proper diagnosis to be made. Even then, a second biopsy in order to obtain material for culture and sensitivity was required. Acid-fast stains should be a routine part of a pathologic examination on inflammatory orbital lesions, particularly with patients taking immunosuppressive therapy. It seems advisable to culture routinely for mycobacteria or keep a small portion of the specimen in the refrigerator in the event that an acid-fast organism is identified on the pathologic material.

The present case also shows the difficulty in therapy with patients who have ocular mycobacterial infection. The patient's orbital abscess took months to improve despite therapy that by sensitivity testing had some effect on the organism in vitro. Brock and associates[15] described a thigh abscess from the *M. fortuitum* complex that took 26 months, and Ward[16] reported a shin lesion in a patient that healed only after two years. Corneal ulcerations caused by this organism are also notorious for their chronicity and difficulty in management.[12] The current organism was resistant to isoniazid, streptomycin, PAS, rifampin, ethambutol, viomycin sulfate, and cycloserine. It seemed to be sensitive to ethionamide and had some sensitivity to erythromycin. Erythromycin was used systemically for several months before any change was observed.

Summary

A 75-year-old woman developed an orbital mass after lacrimal duct probing. Acid-fast bacteria were observed on special stains and *Mycobacterium chelonei,* subspecies *abscessus* was isolated. The patient had been taking systemic corticosteroids.

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A MAKESHIFT RETINOSCOPY RACK

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Ophthalmic bedside examinations and examinations under anesthesia often include retinoscopy. To avoid carrying and using loose trial lenses for this procedure, retinoscopy racks have been developed. However, if one is unavailable, a substitute lens rack can be made easily.

This makeshift retinoscopy rack consists of various trial lenses that are placed into the slots of a nonfrosted, clear plastic, 35-mm slide viewing sheet (Figure). I have used plus and minus lenses in increments of 0.50 and 1.00 diopters, with the plus lenses on one side of the plastic sheet, and the minus lenses on the other side. Also, 10.00 diopter lenses are included for severe hyperopic and severe myopic refractions.

Retinoscopy can be performed through the plastic sheet and lenses while it is held in one hand over the patient's eye. In this manner, a good estimation of the refractive error can be obtained. More precise measurements and confirmation of the initial retinoscopy findings can be made by removing individual lenses from the viewing sheet and by proceeding with the refraction.

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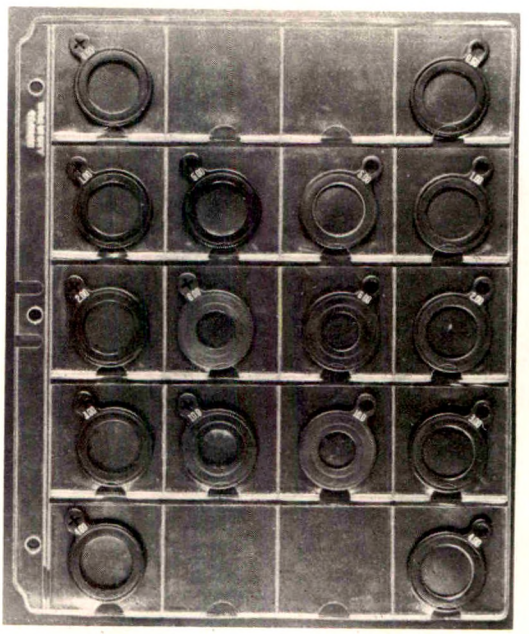

Figure (Wing). Makeshift retinoscopy rack consisting of trial lenses placed into slots of a clear plastic, 35-mm slide viewing sheet.

The retinoscopic reflex is only slightly dulled through the plastic. Glare from the plastic surfaces can be minimized by making small changes in the positioning of the plastic sheet over the patient's eye. Once the examination is finished, the lenses can be returned to the trial lens set in the office.

SUMMARY

A simple makeshift retinoscopy rack consists of various trial lenses placed into the slots of a nonfrosted, 35-mm slide viewing sheet. It is useful in determining the patient's refractive error at the bedside and in the operating room.

MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

IV INTERNATIONAL CHARLOTTENLUND OPHTHALMOLOGICAL CONFERENCE

The IV International Charlottenlund Ophthalmological Conference was held Aug. 28-Sept. 1, 1979, in the beautiful beach resort at Hornbaek, Denmark. Thirty invited ophthalmologists engaged in friendly but spirited round table discussions on a variety of subjects in the frontiers of ophthalmology.

Jürg Draeger, of Bremen, showed some remarkably sensitive and accurate new anesthesiometry equipment. Theodor Waubke spoke on contact metastases with melanomas. Jose Barraquer spoke of dust-free surgery and the need for double running sutures and refractive keratoplasty to prevent epithelial ingrowth. Richard Kratz spoke on control of corneal astigmatism and David McIntyre presented the concept of spiral needles for suturing. Dermot Pierse described new diamond knives only 1.5 mm thick as well as some with five facets which have an almost round end. Alfredo Dominguez of Madrid and Arthur Steele of London spoke on vitrectomy. Jan Worst showed some new fascinating adaptations of the Superblade designs in much smaller sizes for intraocular use.

Jørn Boberg-Ans and Eric Arnott both discussed pupil-centered, posterior chamber lenses. Edward Epstein of South Africa described experiments with soft intraocular lenses in monkeys and in humans. Jonathan Kersley described a four-year follow up of extended-wear contact lenses that he first reported at the III Charlottenlund Conference. He was less than enthusiastic, especially for patients who had to purchase their own lenses. He reported a 24% failure rate; another 24% of the patients who were wearing the lenses had problems but were "addicted." Michael Blumenthal of Israel showed a tucking technique for the surgical repair of a dilated fixed pupil.

John Alpar reminded us that: "To every problem there is an answer that is simple, direct and wrong!"

Most of the speakers made contributions in several areas, both in presentations and, of course, in discussion.

The scientific excellence of these meetings may have been surpassed by the charming and delightful attention we received from our hosts, particularly Jørn and Sonja Boberg-Ans. Even the smallest touches were done with European grace: from flowers in our rooms on arrival to a splendid evening at the castle in Elsinore where a marvelous performance of "Hamlet" was staged by the Old Vic in the castle courtyard.

ROBERT C. DREWS

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AMERICAN ACADEMY OF OPHTHALMOLOGY—1979 MEETING

The American Academy of Ophthalmology Meeting was held in San Francisco Nov. 4-9, 1979. The number of registrants at this meeting approached 14,000, which represents the largest number of ophthalmologists and ophthalmic associates ever to attend a meeting of the American Academy of Ophthalmology. It is probably the largest attendance of ophthalmologists at a single meeting in this country. Hundreds of the registrants were from foreign countries, such as England, France, Italy, Brazil, Argentina, Mexico, Japan, Germany, India, Egypt, Israel, Iran, Sudan, Australia, New Zealand, and China.

The atmosphere was one of joint interest and a great desire to be up-to-date. The many attractions of San Francisco were competition for the cornucopia of information available at this year's meeting. As with previous meetings, there were countless breakfast meetings, luncheon meetings, receptions, alumni meetings, gatherings of old friends, former residents, teachers, colleagues, and recruitment activities.

The scientific meetings took place simultaneously in the three main halls. Often, teaching sessions coincided. Numerous excellent scientific exhibits were available, as well as impressive displays by the technical exhibitors. The new instruments were exciting, some costing the equivalent of two to three or four thousand refractions. It is difficult to recall the old days when mechanical automated refractors and perimeters were not available. How did we ever do it?

Scientific sessions started at 9 A.M. and continued through until 7 P.M. to 10 P.M. each day.

At times, the attendees had to make tough decisions as whether to participate in a course, a major meeting, or see the exhibits; the offerings in each category were most attractive.

The logistics of this meeting offered a

difficult challenge. However, under the statesmanlike leadership of Frederick C. Blodi, president of the American Academy of Ophthalmology, and the extremely competent management of Bruce E. Spivey, executive vice-president and his well-rehearsed staff, the meeting was an outstanding success.

Each of the sessions was kept to a disciplined time schedule. The sessions were chaired by the president, Frederick C. Blodi; the president-elect, Edward W. D. Norton; the first vice-president, Kenneth C. Swan; the second vice-president, Goodwin M. Breinin; and third vice-president, Robert C. Drews. Additionally, there were so many sessions that past presidents, Frank W. Newell, Bradley R. Straatsma, and Kenneth L. Roper were called into presiding action, as well as the councillors, Thomas D. Duane and Whitney G. Sampson; the editor, Stanley M. Truhlsen; and the secretaries, Robert D. Reinecke and David Paton.

Although the official opening did not take place until Monday morning, Nov. 5, scientific sessions were available on Sunday evening, Nov. 4. A combined meeting of the Academy with the Contact Lens Association of Ophthalmologists, dealing with the present status of extended-wear contact lenses and intraocular lenses, drew an overflow crowd. At the same time a combined meeting of the American Association of Certified Orthoptists and the American Orthoptic Council discussed diagnostic and surgical procedures in strabismus surgery; it was also well attended. Concurrently, the American Society of Ocularists considered the problems of enucleation, the imperfect socket, and prosthetics. The impressive attendance at all of these sessions, the night before the opening sessions, was a clear indication of what was going to take place at each of the meetings throughout the week.

The scientific program had something for almost every interest in ophthalmology. Surgery, retinal detachments, cataracts, strabismus, tumors, medical therapy of glaucoma, infections, uveitis, contact lenses, intraocular lenses, new surgical techniques, ocular manifestations of systemic disease, radiological diagnosis, computed tomographic investigations, diabetes, vascular occlusions, and macular edema were all considered. Each subject was considered in depth. Six hundred twenty-three instruction courses, 60 elective scientific exhibits, and 80 scientific posters were provided.

Frederick C. Blodi officiated at the opening session in the large room of the Convention Hall at 9 A.M. on Monday, Nov. 5. After announcements by Bruce Spivey, the honor awards were presented to 32 recipients. The guests of honor, Professors Akira Nakajima of Tokyo, Japan; Frank W. Newell of Chicago; and Gerhard R. E. Meyer-Schwickerath of Essen, Germany, were presented. The Lions International received the Public Service Award.

In presenting the XXXVI Edward Jackson Memorial Lecture, Herbert E. Kaufman discussed the methods of correcting the visual impairments of aphakia, in his characteristically clear, confident, relaxed, and competent style. Spectacle lenses, contact lenses, extended-wear lenses, intraocular lenses, keratomileusis and keratophakia were all considered. He also introduced a method of keratophakia that uses preformed preserved corneal material. This technique might do away with the necessity for complex and expensive computerized lathing equipment. Perhaps, with this method the corneal disk could be prepared at a central laboratory. However, this technique requires long-term evaluation.

Dr. Kaufman also discussed corneal and epithelial replacement as advocated

by Jorge Alvarado and Denis Gaspodarowicz, Gary Greenburg and Steven Kramer. This was a thorough and encouraging summary of the methods, problems, and possibilities for handling aphakia and the complications of aphakia, especially corneal involvements.

An outstanding virology symposium under the direction of Anthony B. Nesburn followed. The symposium was aimed at the busy practitioner of ophthalmology. The speakers updated the knowledge of viral infection and the changing concepts in the pathogenesis of viral disease. Although the adenoviruses, cytomegalic inclusion virus, herpes simplex, and herpes zoster were considered in detail, there was still adequate discussion of slow viruses; for example, Creutzfeldt-Jacob, Scrapie, Kuri and subacute sclerosing panencephalitis.

The role of virus in tumor formation and the influence of immune and antimetabolite therapy were reviewed.

A symposium on ocular trauma and the role of vitrectomy in its management was enhanced by an enlightening discussion of sympathetic ophthalmia by Dr. Blodi.

A huge crowd attended a symposium on the surgical and medical management of glaucoma. It was instructive to learn of the number of side effects that are now encountered with timolol. There also seems to be a general agreement that in time there may be some loss of effectiveness. The early investigations of timolol had suggested freedom from side effects. The experienced glaucoma therapists indicated that the side effects are more frequent than anticipated; these include hallucinations, light-headedness, syncopy, bradycardia, asthma, congestive heart failure, increased blood pressure, headache, eye ache, superficial punctate keratitis, and blurred vision. We learned of these side effects from E. Michael Van Buskirk, Richard P. Wilson, and George Spaeth.

In the program of the Drug Committee of the Academy, George F. Hatch described acute central nervous system disturbance from retrobulbar subdural injections. Richard K. Forster, Richard L. Abbott, and Henry Gelender discussed the management of infectious endopthalmitis with intracameral antibiotics and vitrectomy. John R. Wood, Richard L. Anderson, and James J. Edwards stressed the importance of pressure on the punctum to reduce the systemic absorption of any topically applied agent. Frederick T. Fraunfelder reviewed some of the side effects of timolol that had been reported to the National Registry of Induced Ocular Side Effects as well as those of other drugs. Theodore Krupin, Barry Silverstein, and Bernard Becker described the topical hypotensive action of antazoline. Frank Dea, John Valentine, and Irving H. Leopold discussed how aspirin taken orally can appear in measurable quantities in the tears. Roswell R. Pfister pointed out that ascorbic acid may be helpful in the treatment of ocular alkali burns. Antiproteolytic enzymes' presence in human tears was noted by Janet Anderson. Anthony Bron, a guest of the Drug Committee, gave a delightful presentation of the management of corneal disease.

There was a symposium on ocular inflammations and uveitis and conditions associated with dermatologic disorders. At the same time, there was a symposium in conjunction with the ophthalmology section of the Council of the American Medical Association, chaired by Thomas D. Duane, co-chaired by Oliver H. Dabezies, in which Alfred Kopf was introduced by Joseph Wadsworth. Dr. Kopf presented the Parker Heath Memorial Lecture. It was a detailed and

thorough discussion of cutaneous malignant melanoma and a multivariant computer analysis of the many factors that can accurately predict the outcome. These varients include the histologic features, such as thickness, mitosis per square millimeter, and melanin content. Also covered were clinical aspects, such as size, location, and surface characteristics. Lorenz Zimmerman illustrated the manner in which ocular melanotic tumors differed and resembled skin tumors. Diagnostic and therapeutic approaches were evaluated together with the nature and course of untreated melanoma.

Concurrently, methods of evaluating retinal function were scrutinized.

Neovascular glaucoma was considered in detail in a meeting of the National Society to Prevent Blindness. The program was set up by Alan Kolker. Particular attention was paid to the management of aphakic individuals with glaucoma. The program of the American Society of Ophthalmic Registered Nurses was coordinated by Heather Boyd-Monk. Vitrectomies were considered in depth at a meeting organized by Mackenzie Freeman. The role of vitrectomies was detailed in cystoid macular edema in diabetic patients with traction retinal detachments, in endophthalmitis, and in diagnosis of lymphoma.

Cystoid macular edema, Purtscher's disease, retinal hemorrhages, vascular occlusions, orally administered fluorescein, angiogenesis factor, a variety of diabetic retinopathies, and the use of intracameral hyaluronic acid were discussed.

The symposium on radiologic analyses and computed tomographic ophthalmographic investigations of muscles, optic nerves, orbital tumors, and lacrimal gland tumors was well presented. The prognosis and management of these conditions were considered in depth.

A joint meeting of the American Association of Ophthalmology considered the impact of federal regulations on ophthalmologic care.

At the meeting of the American Intraocular Implant Society, a huge audience gave a great deal of attention to the intraocular lens implants. Results in over 100,000 intraocular lens implantations were reviewed by the Advisory Ophthalmic Device Section of the Food and Drug Administration, presented by its chairman, David Worthen. At this same session a symposium considered intracapsular vs extracapsular extraction for intraocular lens implantation. Norman Jaffe made the Ridley 30th anniversary presentation and Henry Hirschman delivered the Fifth Binkhorst lecture. Dr. Hirschman suggested that the 1980s will be a decade of the lens implant, but with a strong trend toward the use of extended-wear contact lenses. He anticipated that there will be significantly fewer spectacle lenses used for the correction of aphakia in the next decade. There was a meeting for those interested in keratoplasty, the storage and preservation of corneal material for grafting.

Tumors and reconstruction of the eyelids were considered in detail. Aspects of pediatric ophthalmology were covered. A combined meeting of the Castroviejo and the International Corneal Societies discussed anterior-segment surgery in relation to trauma, intraocular lens, endothelial transplantation, the effects of growth factor on wound healing, methods of evaluating stress on a corneal wound, and techniques for handling keratophakia.

The session finished on Friday morning with a combined meeting of the David J. Kelman Research Foundation and the American Intraocular Implant Society. Though this was the last day of the Academy meeting, the Implant Soci-

ety planned to continue their meeting for the next two days. Lawrence Pape and Endré A. Balazs discussed the use of hyaluronic acid, as did David Miller and Robert Stegman, on intraocular lens implant and its effect on the ocular tissues. Anterior chamber fluorophotometry, as a measurement of retinal vessel leakage in diabetic patients was critiqued. Consideration was given to extraction of displaced cataracts, cataracts in the presence of detachments, glaucoma, uveitis, and vitreal disease. Edward Fetherolf, Miles Galin, Ira Goldstein, and Robert Buys explained the induction of inflammation caused by the intraocular lenses.

The exhibit, "Racket Sports and Eye Injuries—Are They Preventable," by Michael Easterbrook, was selected as the prize winner, but it was only one of many excellent scientific exhibits. The meeting provided a great opportunity for each ophthalmologist to fill gaps in knowledge, acquire new information, and strengthen knowledge gained in the distant and recent past. This was a most convincing proof of the constant, strong desire and effort of ophthalmologists to be prepared to handle their patient problems.

Could the meeting be improved? Of course there are always suggestions for that, but I doubt it. Initially it seemed overwhelming in its scope, but as the week wore on, participants began to handle the information challenge with ease and expertise. Possibly a greater effort in selection of material and fewer simultaneous sessions could make it easier for an individual who has difficulty selecting where to go, as each of the papers presented is not of equal quality. However, there is no way to eliminate attractive papers fairly. An attempt by a special Academy Selection Committee could be made, but I doubt whether they could do a better job. It is much simpler for the specialist, of course, to be able to select, whereas the generalist who wants to gather as much information as possible in many areas, has pressure and strain in trying to get the most out of this tremendous amount of information. However, even this could be handled by a careful perusal of the program and the selection of the areas one wants to attend, well in advance of the meeting time. True, the attendee may have to stand at some of the sessions, as he moves from one hall to another, but this is a small price to pay in order to have such a wonderful array of exciting new information.

Edward W. D. Norton will be the president of next year's Academy. David Shoch is the president-elect and Theodore Steinberg has been elected the new councillor for the Academy. Jerome Bettman is first vice-president, Alice R. McPherson is second vice-president, and Fred M. Wilson is third vice-president. Robert D. Reinecke is the designated representative delegate for Washington affairs; secretary for instruction is Melvin L. Rubin; secretary for continuing education is David Paton. Paul Henkind replaces Stanley M. Truhlsen as editor for Ophthalmology. Whitney G. Sampson will continue as councillor through 1980; Marshall M. Parks, councillor through 1981; and Thomas D. Duane as councillor through 1982. Under the guidance of these officers, plans are underway for the next annual meeting of the Academy in New Orleans, Nov. 13-17, 1980. The 1981 meeting will be held in Atlanta, Georgia, Nov. 1-5. In 1982, in San Francisco, will be a combined meeting of the American Academy of Ophthalmology and the XXIV International Congress of Ophthalmology Oct. 31- Nov. 5, 1982. By that time this Academy will have vast experience in handling huge crowds of attentive, information-craving ophthal-

mologists. The new San Francisco convention center and facilities should be completed in ample time for the meeting.

IRVING H. LEOPOLD

OBITUARY

Samuel J. Kimura, M.D. 1912–1979

Samuel J. Kimura, professor of ophthalmology emeritus at the University of California's School of Medicine in San Francisco, died unexpectedly in Granada, Spain, Oct. 15, 1979. His many friends and professional colleagues mourn the passing of a gifted teacher, a superb physician, and an innovative researcher.

Dr. Kimura was born in Stockton, California, on April 21, 1912. After graduation from high school, he entered the University of California at Berkeley where he obtained both the Bachelor of Arts and the Master of Science (anatomy) degrees. He received his M.D. degree from the University of California in 1940, and after a year of internship in Chicago he joined the Army, serving in the Medical Corps in southern Europe. He later returned to California to enter the ophthalmic residency program of the late Frederick C. Cordes, M.D., in San Francisco. While in this program he made his first contacts with Phillips Thygeson, M.D., and the late Michael J. Hogan, M.D., men who were to influence his later career in inflammatory diseases of the eye.

Dr. Kimura was known for his many contributions to the fields of uveitis and external diseases of the eye. In collaboration with other members of the Francis I. Proctor Foundation for Research in Ophthalmology, he established the importance of lysozyme deficiency in keratoconjunctivitis sicca; he demonstrated the presence of herpes virus in the corneal epithelium by means of fluorescein-tagged antibody; he made significant observations on the pathogenesis of herpetic uveitis and on Fuchs' heterochromic iridocyclitis; he studied and classified many forms of uveitis associated with inflammatory joint diseases; and he contributed to highly significant studies on toxoplasmic retinochoroiditis. Most recently he and Robert Weinreb, M.D., showed the importance of angiotensin converting enzyme in the diagnosis of sarcoid uveitis. He was the developer of a flexible metal spatula for the performance of diagnostic scrapings of the conjunctival epithelium, and this instrument still bears his name.

He was a member of many scientific societies including the Association for Research in Vision and Ophthalmology

(of which he was once secretary-treasurer), the American Ophthalmological Society, and the American Medical Association. He was a member of the course faculty of the American Academy of Ophthalmology and will be sorely missed in that organization. He was President of That Man May See, Inc., a private fund-raising organization dedicated to the support of eye research.

Dr. Kimura is survived by his wife, Pearl Kimura, who was also severely injured in the same automobile accident that ultimately took Dr. Kimura's life. Those of us who knew and worked with Sam look with sorrow on the passing of a dedicated ophthalmologist and a true friend. We extend our sympathy to Mrs. Kimura and to Dr. Kimura's sole surviving sister, Mrs. Oscar Rambo of San Francisco.

G. RICHARD O'CONNOR

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Chloroquine Retinopathy

Editor:

"Long-term course of chloroquine retinopathy after cessation of medication" (Am. J. Ophthalmol. 88:1, 1979), J. R. Brinkley, E. L. Dubois, and S. J. Ryan described follow-up of their patients with serial visual acuities, tangent fields to discover constriction and paracentral scotomas, and fluorescein angiograms to evaluate possible retinal damage. Although they were able to establish a general lack of progressive damage in their patients, these tests will mainly detect damage once it has become irreversible.

We have been observing many patients who take chloroquine hydroxychloroquine for collagen-vascular disease. We have used the electro-oculogram as well as the above methods. We obtain baseline studies at the time chloroquine is begun and repeat values every four months while the patient is taking the medication. When compared to their baseline values, most of the patients initially demonstrate a supranormal light:dark ratio in the 250 to 350% range. If we then see a drop to below normal values (< 180) we recommend discountinuing the drug. However, we have found that the drug can be restarted at lower dosages, though the patient may have a supranormal light:dark ratio. No change has been found in visual acuity, visual fields, and in the maculae in the patients in whom this course has been followed.

Finally we also have had one patient who received antimalarial chloroquine therapy 20 years ago, and who has developed central aerolar sclerosis. The patient had an otherwise unremarkable family and medical history. If there are other cases on record, it would be valuable to report them to Frederick Fraunfelder, M.D., University of Oregon, 3181 S.W. Sam Jackson Road, Portland, OR 97201, so that this association can be studied more closely.

The electro-oculogram is a useful tool in detecting chloroquine toxocity and may be useful in regulating the dosage, and in preventing irreversible damage.

JOHN R. HECKENLIVELY, M.D.
DEIDRE MARTIN
AND
JOSHUA LEVY, M.D.
Los Angeles, California

Reply

Editor:

We agree with the observations of Dr. Heckenlively, Ms. Martin, and Dr. Levy,

that the electro-oculogram is an excellent method of detecting early chloroquine damage when it is still in the reversible stage. That the first change in the electro-oculogram is a supranormal light:dark ratio has been observed in our electro-physiology laboratory at the Estelle Doheny Eye Foundation (Thomas Ogden, M.D., personal communication). Reversible subnormal ratios have been reported in chloroquine retinopathy as well.[1] We did not do electro-oculography on the patients in our study because we were attempting to compare factors that had been measured ten years previously when such testing was not available in our institution.

We have begun a study to determine if chloroquine retinopathy patients with abnormal electro-oculograms but normal Goldmann fields might have more subtle field changes detectable by computed (Octopus) perimetry.

JAMES R. BRINKLEY, JR., M.D.
EDMUND L. DU BOIS, M.D.
AND
STEPHEN J. RYAN, M.D.
Los Angeles, California

REFERENCE

1. Arden, G. B., Friedmann, A., and Kolb, H.: Anticipation of chloroquine retinopathy. Lancet 1:1164, 1962.

Retinal Detachment in Pseudophakia

Editor:

In the introduction of their recent article, "Retinal detachment in pseudophakia" (Am. J. Ophthalmol. 88:49, 1979), M. A. Galin, T. A. Poole, and S. A. Obstbaum point out that although intraocular lenses might reduce the incidence of detachment, this has "not been statistically validated." Unfortunately their own sample is too small to decide the issue.

The incidence of retinal detachment during the year following routine cataract extraction is generally estimated to be 2%. By studying 150 patients without implants the authors observed exactly what they could have predicted: three detachments. If implants reduced this incidence by even 50%, a sizeable improvement, they could have predicted one to two cases in the implant group as well, even if chance variation were somehow eliminated. The expected reduction, from three to one or two cases out of 150 at best, would hardly have been considered significant. At worst, chance variation might have resulted in more detachments in the implant than nonimplant group.

Three factors influence the sample size required to demonstrate a difference between two groups[1]: the magnitude of the difference one wishes to demonstrate; the level of statistical significance one is seeking (for example, $P < .05$, $< .01$, and the like); and the risk one accepts that chance variation might obscure a real difference. Simple formulae exist for computing sample size under varying conditions.[2] As a convenient rule of thumb, to demonstrate a 50% reduction in a particular occurrence requires 40 occurrences (for example, retinal detachments) in the group at highest risk; a reduction of over 90% requires 12 occurrences. To accumulate 40 retinal detachments 2,000 routine cataract extractions (plus 2,000 postimplant patients for comparison) would have to be followed up; to accumulate 12 detachments, 600 would have to be followed up. Although following up 600 patients in each group is obviously easier than following up 2,000, failure to demonstrate any difference would result in the more limited conclusion that pseudophakos is unlikely to reduce the incidence of postoperative retinal detachment by at least 90%.

ALFRED SOMMER, M.D.
Baltimore, Maryland

REFERENCES

1. Sommer, A.: Toward a better understanding of medical reports.. Am. J. Ophthalmol. 79:1053, 1975.
2. ———: Epidemiology and Statistics for the Ophthalmologist. Oxford, Oxford University Press. In press.

Reply

Editor:

Dr. Sommer's points are well taken and, indeed, we were aware that impressions concerning the reduction of retinal detachments by implants were not statistically validated. We further agree that the data in our on-going study are from a woefully small sample and are not statistically meaningful.

Unfortunately, the population that undergoes the procedures is an elderly one and the opportunity for any single group to obtain sufficient follow-up data is difficult. Perhaps the sample sizes Dr. Sommer recommends for statistical validity might be obtained from a pooled study such as the present investigations of the Food and Drug Administration. If sufficient controls have been obtained, the sample of this multifaceted study would be more than adequate to provide statistical validity.

MILES A. GALIN, M.D.
THOMAS A. POOLE, M.D.
AND
STEPHEN A. OBSTBAUM, M.D.
New York, New York

Keratoprosthesis

Editor:

I was pleased to see keratoprosthesis, a neglected subject, described in the article, "Results of keratoprosthesis" (Am. J. Ophthalmol. 88:190, 1979), by G. N. Rao, H. L. Blatt, and J. M. Aquavella. My own experience goes back almost 20 years; since 1967 I have been using my own two-piece perforating keratoprosthesis.

I wish to congratulate the authors on the success they have obtained in patients for whom there was otherwise no hope. I endorse their view that "the best results have been obtained where keratoprosthesis has been the initial procedure." Too often in my experience one or more keratoplasties that could not possibly succeed have nevertheless been carried out, thus lowering the vitality of the recipient eye, making keratoprosthesis surgery less likely to succeed.

I congratulate them also on the absence of extrusion. I wish I could say the same. A significant number of my 135 patients operated on since 1967 have extruded the keratroprosthesis. The danger period seems to be within the first few months or considerably later on, particularly if the patient is elderly and diabetic. I learned early that prescribing corticosteroids either orally or locally was unwise; thus I was surprised to see the authors are prepared to use large doses of orally administered corticosteroids.

I have not been concerned with retroprosthetic membrane formation, provided that the anterior segment was thoroughly "gutted" when the keratoprosthesis was inserted. When membrane formation has occurred, access to it is obtained by unscrewing the central cylinder.

I was particularly impressed with the success the authors achieved in cases of the dry eye syndrome.

D. P. CHOYCE, M.S., F.R.C.S.
Essex, England

Reply

Editor:

Over the past two decades the pioneering efforts of Peter Choyce in the field of keratoprosthesis have contributed significantly to our recent success with

this procedure. We are pleased that Dr. Choyce endorses our general views on the procedure of keratoprosthesis.

Fortunately, in our series, we encountered the problem of extrusion only recently, when we had extrusion in one of our patients 2½ years after through and through keratoprosthesis. We believe that our success with this procedure in terms of extrusion is probably due to two factors. One is the keratoprosthesis is brought out through the eyelid and the support afforded by the eyelids keeps the prosthesis in position. The other factor is the periosteal support around the prosthesis covering the surface of the cornea and around the optical cylinder.

As to the question of giving corticosteriods orally in high dosages, the rationale is the considerably high incidence of postoperative vitritis that occurs in these patients. This is probably related to the surgical trauma associated with performing this procedure. The only way of controlling such intensive inflammatory reactions is with orally administered corticosteroids, using standard precautions. We did not encounter any problems in our patients. However, even high dosages of corticosteroids did not prevent the development of retroprosthetic membrane.

Differences in the nature of our prosthesis, its chemical composition, or the manner of sterilization may account for the high incidence of inflammation and membrane formation.

Retroprosthetic membrane has been one of our main problems despite a thorough anterior vitrectomy and cleaning of the anterior segment before the insertion of the keratoprosthesis.

When the complication develops, we use the same procedure advocated by Dr. Choyce; that is, take out the central opitical cylinder and remove the retroprosthetic membrane utilizing a vitreous suction cutting device. However, in some of the cases, the retroprosthetic membrane is thick and thus excision is difficult.

GULLAPALLI N. RAO, M.D.
Rochester, New York

BOOK REVIEWS

The Systemic Manifestations of Temporal Arteritis. By Louis A. Healey, Kenneth R. Wilske. New York, Grune and Stratton, Inc. Hardcover, 140 pages, index, 11 tables, 15 black and white figures. $12.50

This monograph is a complete exposition of the current knowledge on the subject of giant cell (temporal) arteritis and of its relationship with polymyalgia rheumatica. The authors have had a long and extensive experience with this puzzling set of conditions and have thoroughly examined the voluminous bibliography pertinent to it. They call attention to the evidences that polymyalgia rheumatica may occur in the absence of giant cell arteritis, may precede and later develop into giant cell arteritis, may coexist, or may be absent.

The ten chapters begin with a historical review. The other chapters are as folows: clinical manifestations of giant cell arteritis, ophthalmologic manifestations, clinical picture of polymyalgia rheumatica, relationship between these two conditions, relationship of giant cell arteritis to other types of vasculitis, the etiologic factors, the pathology, the laboratory findings, and the treatment.

What emerges from this monograph are the concepts that there is a close relationship between giant cell arteritis and polymyalgia rheumatica, that the cause is unknown, and that when present arteritis may involve not only the extracranial and orbital arteries but also the aorta and its major branches to the heart

and extremities. Except under unusual circumstances of death from coronary occlusion, heart failure or cardiac rupture, the most devastating manifestation of giant cell arteritis is that of sudden onset of permanent blindness in one or both eyes caused by ischemic optic neuritis. The pain accompanying polymyalgia rheumatica seems to be its major manifestation.

The authors quote the incidence of blindness, which ranges in various reports from 6 and 8% to 60%. The authors believe the incidence to be more often in the 6 to 8% range, on the basis of reports of their own series in 1977, and of others of 1972 and 1978. However, the authors fail to take into account that all reports in these latter years are biased toward a lower incidence of blindness than occurs during the natural course of the disease. The incidence of blindness now is greatly reduced because of increased awareness of the disease, much earlier diagnosis, the discovery of the highly effective treatment with the corticosteroids in October 1949 at the Mayo Clinic, and the recognition of the spectrum of polymyalgia rheumatica as a significant forerunner or accompaniment of giant cell arteritis.

Of the 175 consecutive cases which I reported in 1960, comprising all the patients with temporal arteritis seen at the Mayo Clinic from 1931 through 1957, there was an overall incidence of loss of vision in one or both eyes of 42%. Forty-five of these patients were seen before October 1949. In this untreated group, the incidence of blindness in one eye was 24% and in both eyes was 29%, a total incidence of 53%. The other 130 patients seen after corticosteroid treatment became available still included a high incidence of 36% blindness. Many of this latter group of patients came to the Mayo Clinic long after they became blind.

The risks to vision of a delay in diagnosis and treatment are so great that a clinician must have no doubt but that over half his patients will lose vision unless promptly treated.

Despite the exception noted above, this text is excellent. The book should be available to every medical student, internist, neurologist, ophthalmologist and family practitioner, since only by a thorough knowledge of this subject can the devastating visual involvement of giant cell arteritis be prevented.

ROBERT W. HOLLENHORST

Phacoemulsification and Aspiration of Cataracts. By Jared M. Emory and James H. Little. St. Louis, C. V. Mosby, 1979. Hardcover, 325 pages, foreword, preface, table of contents, 507 black and white figures, 1 color plate. $42.50

This is a thorough, beautifully illustrated presentation of current knowledge concerning the phakoemulsification of cataract. Proper credit is given to the inovator, Charles Kelman, who gives a brief summary of the development of the system.. This is followed by a detailed review of the instrumentation available, the methods of obtaining preliminary experience in animal models, and a description of the types of patients suitable for emulsification. The authors emphasize the importance of thorough training in microsurgery before embarking on the procedure. They present detailed data concerning preperative preparation, medication, and anesthesia. Technical points of the sequential steps from incision to wound closure are graphically illustrated in an exceptionally clear manner with both photographs and line drawings.

Special chapters describe the manage-

ment of congenital cataracts, traumatic cataracts, subluxated lenses and combinations of phakoemulsification procedures with glaucoma operations, corneal transplants, and intraocular lens insertion. The prevention and management of operative and postoperative complications is well covered. Of particular value are the tabulations of the results obtained by various surgeons and the inclusion of an extensive bibliography, which will be useful to any serious student of cataract surgery. Although the text refers mainly to the Kelman phakoemulsification technique, several chapters are also devoted to the Girard phaco-fragmentation system.

This is the most comprehensive review of phakoemulsification and lens aspiration techniques I have encountered. I recommend it to anyone interested in cataract surgery, particularly those who want to enter or re-enter the field of extracapsular surgery.

A. GERARD DEVOE

Colour Atlas of Ophthalmology. By Arthur Lim Siew Ming and Ian J. Constable. Boston, Houghton Mifflin Professional Publishers, 1979. Hardcover, 151 pages, preface, table of contents, index, 11 black and white figures, 182 color figures. $10

Drs. Lim and Constable prepared this handy and inexpensive color atlas of ophthalmology for students, paramedical personnel, and physicians interested in common eye diseases.

The authors briefly described most common ocular problems; they described the most important ophthalmologic diseases in greater detail. The brevity of the text sometimes leads to inaccuracies, such as, in the description of retinal detachment: "tears cause separation of the retina from the choroid."

There is an excellent distribution of external and fundus photographs, most of high quality. Not only did the authors include such entities as diabetic retinopathy, papilledema, disk cupping, and retinal vessel closure, but they further provided photographs of basic findings, which will be most helpful for the less experienced clinician. These include chalazion, white pupillary reflex, dense cataract, hyphema, and extraocular muscle palsy. Drs. Lee and Constable have prepared a fine, brief atlas and text that deals with ophthalmologic disease on a practical level.

ALBERT S. LEVEILLE

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Arthritis and Rheumatism

OPHTHALMOLOGIC SAFETY OF LONG-TERM HYDROXYCHLOROQUINE TREATMENT. Rynes, R. I., Krohel, G., Falbo, A., Reinecke, R., Wolfe, B., and Bartholomew, L. E. (Div. Rheumatol., Dept. Med. and Dept. Ophthalmol., Albany Med. College, Albany, N.Y.). Arthritis Rheum. 22:832, 1979.

Antimalarials of the 4-aminoquinolone group have been found to be effective in the treatment of rheumatoid arthritis but there have been many reports of retinal toxicity from the use of chloroquine. More recently hydroxychloroquine has become the drug of choice and the authors feel that this is a less toxic drug. They followed 99 patients receiving 400 mg a day of hydroxychloroquine and found that no patient developed significant loss of vision or visual field constriction to a white test object. However, three patients did have evidence of toxicity but the medication had to be permanently discontinued in only one. The authors recommend that before starting hydroxychloroquine all patients be questioned about visual symptoms and have evaluation of their visual acuity, fundi and a tangent screen test with a 5 mm red and 3 mm white at 1 m. These tests should all be repeated at six-month intervals while the patient is being treated with hydroxychloroquine. (1 figure, 1 table, 33 references)—David Shoch

British Journal of Ophthalmology

SILICONE OIL IN THE TREATMENT OF MASSIVE PRERETINAL RETRACTION. I. RESULTS IN 105 EYES. Grey, R. H. B., and Leaver, P. K. (Retinal Unit, Moorfields Eye Hosp., City Road, London). Br. J. Ophthalmol. 63:355, 1979.

From an approximate total of 1,500 cases undergoing retinal surgery 105 eyes were selected for treatment with intraocular silicone oil injections. The selection was based on the ophthalmoscopic signs of massive preretinal retraction and on the fact that retinal shortening and rigidity made reattachment by conventional surgical means impossible. Ninety-two of these eyes had previously undergone conventional retinal surgery without avail. The status after the silicone oil injection could be assessed in 93 eyes for one year or longer. A case was judged to be anatomically successful if more than half of the retina including the posterior pole had become reattached. Such anatomical success was recorded in 67 eyes within one month after surgery and lasted in 51 eyes throughout the follow-up period. Anatomical success was associated with improvement in visual acuity, most frequently from a preoperative level of hand movements at 1 m to finger counting at the same distance. (5 figures, 7 tables, 14 references)—Peter C. Kronfeld

SILICONE OIL INJECTIONS IN THE TREATMENT OF MASSIVE PRERETINAL RETRACTION. II. LATE COMPLICATIONS IN 93 EYES. Leaver, P. K., Grey, R. H. B., and Garner, A. (Retinal Unit, Moorfields Eye Hosp., City Road, and Dept. Pathol., Inst. Ophthalmol., Judd Street, London). Br. J. Ophthalmol. 63:361, 1979.

The preceding paper dealt with the functional results obtained with intraocular silicone oil injections in eyes deemed unsuitable for conventional detachment surgery because of rigidity and shortening of the retina. In the present paper the authors report on late complications of silicone oil injection observed during follow-up periods of up to four years. Slowly developing lens opacities were the most common complication. Glaucoma was relatively rare (14 out of 93 eyes) and in more than half of the cases was probably preexistent to the treatment. Minute globules of silicone were identified in the chamber angle in many eyes. Single large oil bubbles in the anterior chamber gave rise to band-shaped keratopathy in five out of six eyes. Only one, soft, blind, painful eye had to be removed. There was no clear-cut evidence of a toxic effect of silicone on the retina. (10 figures, 3 tables, 11 references)—Peter C. Kronfeld

TREATMENT OF AMOEBOID HERPETIC ULCERS WITH ADENINE ARABINOSIDE OR TRIFLUOROTHYMIDINE. Coster, D. J., Jones, B. R., and McGill, J. I. (Dept. Clin. Ophthalmol., Inst. Ophthalmol., Moorfields Eye Hosp., London). Br. J. Ophthalmol. 63:418, 1979.

For this comparison of two antiviral agents amoeboid herpetic ulcers were chosen because they have often been treated with steroids before referral to an ophthalmologist; besides, many have associated stromal disease and uveitis, and constitute therefore the most difficult therapeutic challenge for antiviral drugs used for ulcerative (epithelial) herpetic keratitis. The coded preparations were randomly allocated by the pharmacist within closely matched strata related to poor prognosis, namely, size of the epithelial defect, whether or not the patient had been treated with topical steroids before entering the study and whether or not he was atopic. The coded medications were either 3.3% adenine arabinoside ointment (Ara-A) or 1% trifluorothymidine eye drops, both applied five times a day. Patients receiving topical steroids were weaned from them over the first three days of the new treatment. At the follow-up examinations on alternate days in the outpatient department the ulcer was drawn and measured with an attachment to the Haag-Streit slitlamp, the extent of the stromal disease was assessed and signs of local toxicity of the antiviral agents were looked for. The treatment was judged to have failed if the epithelial defect (1) had not healed after 21 days, (2) had failed to decrease in size or (3) had enlarged over three consecutive days. Out of a total of 87 eyes six ulcers failed to heal, four of which were in the Ara-A group and characterized by progression of the stromal disease. Statistically, trifluorothymidine appeared to be more effective than Ara-A. (5 figures, 6 references)—Peter C. Kronfeld

CATARACT EXTRACTION COMPLICATED BY CAPSULAR GLAUCOMA. Dark, A. J. (Dept. Ophthalmol., Veterans Administration Hosp., Syracuse, N.Y.). Br. J. Ophthalmol. 63:465, 1979.

In eyes with capsular glaucoma accumulation of pseudoexfoliation fibers has been known to occur embedded in the anterior limiting layer of the iris as well as in the circumferential furrows of the posterior iris surface. In the latter location this material may cause adhesions to the peripheral lens capsule and could play a role in causing rupture of the capsule during cataract extraction. Six surgically (without gross capsule rupture) obtained lenses form the basis of the present report. Macroscopically, sheets of iris pigment epithelium were found adherent to preequatorial portions of the lens capsule. Transmission electron microscopy disclosed bonding of iris pigment to zonular fibers, to the lens capsule and to multilaminar, partly dehiscent basement membranes of pigment epithelial cells. This bonding suggests possibilities of interference with physiological functions such as aqueous flow as well as with the mechanics of cataract extraction. (4 figures, 13 references)—Peter C. Kronfeld

THE FISHMOUTH PHENOMENON IN RETINAL DETACHMENT: OLD CONCEPTS REVISITED. Birchall, C. R. (Dept. Ophthalmol., Aberdeen Royal Infir. and Woodend Hosp., Aberdeen, Scotland). Br. J. Ophthalmol. 63:507, 1979.

In eight patients with retinal detachment a prominent feature of the primary pathological process had been a large posterior horseshoe-shaped tear which had responded to cryopexy and a circumferential buckle with persistence of the detachment and transformation of the tear into a fishmouth (i.e., reduction in circumferential direction with greater elevation of the operculum). The author's reoperation consisted of the following steps: (1) removal of all encircling tapes and explants; (2) cryotherapy applied to the area of the tear or tears and over a wide surrounding area equivalent to a ring external to any previous cryotheraspy; (3) release of subretinal fluid at a point distant from the tears; (4) keeping the eye relatively normotensive by means of external pressure with a cotton applicator, sterile air is injected through a pars plana incision to a level where the eye is still soft; (5) a No. 40 silicone band is placed underneath the rectus muscles and secured at the equator or behind it in quadrants where a tear straddles the equator. The tape does not indent over any of the tears and no implant or explant is used to buckle the sclera. The retina reattached in all eight cases. (4 figures, 13 references)—Peter C. Kronfeld

RETINOBLASTOMA: CORRELATION OF INVASION OF THE OPTIC NERVE AND CHOROID WITH PROGNOSIS AND ME-

TASTASES. Stannard, C., Lipper, S., Sealy, R., and Sevel, D. (Depts. Radiotherapy, Pathol., and Ophthalmol., Groote Schuur Hosp., and Univ. of Cape Town, South Africa). Br. J. Ophthalmol. 63:560, 1979.

On the basis of clinical examination of 95 patients with retinoblastoma and histological material in 74 of these patients, the authors propose a partly new classification in which the stage of the disease is correlated with the histologically determined extent of uveal and optic nerve invasion by tumor tissue. Four stages are differentiated: I—lesions amenable to local therapy and treated conservatively aiming at preserving vision; II—lesions unsuitable for conservative local therapy but still ostensibly confined to the eye and its orbit; III—lesions which have spread to local lymph nodes, adjacent bones or to the central nervous system, but have not given rise to blood-borne metastases; IV—the stage of hematogenous metastases. In bilateral cases the eye with the more advanced disease is chosen to represent the patient. All cases were followed for a minimum of three years or until death. In the subgroup of 25 cases (of stage II) in which the resection line was posterior to the level of nerve invasion and the uveal involvement did not extend beyond the choroid proper, every patient survived. The prognosis became considerably worse once the sclera or anterior uvea were involved. Iris involvement reflected advanced disease and was closely associated with hematogenous dissemination. A parallel could be drawn between retinoblastoma and Wilms's tumor in that patients under the age of two years had a better prognosis. (10 tables, 44 references)—Peter C. Kronfeld

British Medical Journal

BLINDNESS AFTER TREATMENT FOR MALIGNANT HYPERTENSION. Cove, D. H., Seddon, M., Fletcher, R. F., and Dukes, D. C. (Dudley Road Hosp., Birmingham, England). Br. Med. J. 2:245, 1979.

Two young women in their early 30s were seen with Grade 4 hypertensive retinopathy and markedly elevated blood pressures. In both cases the pressures were acutely dropped with drugs, different drugs being used in the two cases. In the first case the pressure was dropped over a 24-hour period but in the second the pressure was dropped very abruptly. In both cases there was a sudden onset of total blindness with fixed dilated pupils. The vision did not recover in either patient. It is felt that ischemia of the optic nerve heads developed from a fall in perfusion pressure in tissue with high interstitial pressure due to preexisting edema. The authors advise a very slow, careful reduction of the blood pressure in people with malignant hypertension. (1 figure, 4 references)—David Shoch

Journal of Neurology, Neurosurgery and Psychiatry

SUBTLE DISTURBANCES OF VISION AFTER OPTIC NEURITIS ELICITED BY STUDYING CONTRAST SENSITIVITY. Zimmern, R. L., Campbell, F. W., and Wilkinson, I. M. S. (Dept. Neurol., Addenbrooke's Hosp., Cambridge Univ., Cambridge, Mass.). J. Neurol., Neurosurg., Psychiatry 42:407, 1979.

The eight patients described here had all recovered from episodes of optic neuritis and in seven of the eight cases the vision had returned to 6/6 (20/20), in one case it was 6/9 (20/30). Some of the patients had afferent pupillary defects and all had delays in the visual evoked response. The authors show that in addition to this, a definite abnormality could be demonstrated in the ability to detect contrast. Targets were presented on a television screen and the number of the cycles/degree varied from 20 to two-tenths of a cycle per degree. In all cases the contrast sensitivity function was well below that obtained in the unaffected eyes. It appears that certain disorders of vision are associated with an abnormality of the contrast sensitivity function in spite of near normal visual acuity. Such an abnormality may affect pattern recognition without having an influence on Snellen acuity because of the high contrast of the latter and its predominant association with the higher spatial frequencies. Contrast sensitivity function is thus the only tool available to study those aspects of vision which have remained impervious to other subjective tests of visual function. (3 figures, 1 table, 13 references)—David Shoch

Journal of Pediatric Ophthalmology and Strabismus

MIOTICS VS GLASSES IN ESODEVIATION. Hiatt, R. L., Ringer, C., and Cope-Troupe, C. (Dept. Ophthalmol., Univ. Tennessee Ctr. for Health Sci., Memphis, Tenn.). J. Pediatr. Ophthalmol. Strabismus 16:213, 1979.

Twenty-three children with esotropia and variable amounts of hyperopia underwent treatment with phospholine iodide 0.125% daily for two months, and then with full hyperopic spectacle correction (as determined by atropine refraction) or visa versa. One child had a larger reduction in the esodeviation with miotics than with glasses, 11 showed no difference and 11 had a larger reduction in the esodeviation with glasses than with miotics. (1 table, 19 references)—Paul E. Romano

OPTIC NERVE APLASIA AND HYPOPLASIA. Hotchkiss, M. L., and Green, W. R. (Eye Pathol. Lab., Wilmer Inst., and Dept. Pathol., Johns Hopkins Med. Inst., Baltimore, Md.). J. Pediatr. Ophthalmol. Strabismus 16:225, 1979.

The clinical and histopathologic features of three cases of optic nerve aplasia and 22 cases (35 eyes) with hypoplasia were studied and collated. The authors suggest that optic nerve aplasia and hypoplasia lie along a spectrum of defective ocular development. The clinical histopathologic picture that composes optic nerve hypoplasia (i.e., complete or partial absence of normal optic nerve tissue components with or without the presence of retinal vasculature) results from an insult to the CNS with subsequent atrophy of previously-developing nerve fibers. A similar, although more discrete, insult sustained earlier in the maturational sequence could account for an aplastic optic nerve, involving a total absence of optic nerve fibers and retinal vessels. Since the vulnerable period for such a critically-timed disruption is more narrow, one would expect the occurrence of aplasia to be less frequent than hypoplasia. This has been observed. A genetic event, whether inherited or mutational, might result in either aplasia or hypoplasia, depending on its precise nature. Environmental factors such as drugs and trauma cannot be ruled out as primary causative factors behind both the optic nerve anomalies and the more general CNS disturbances. (18 figures, 6 tables, 26 references)—Paul E. Romano

BENIGN TUMORS OF THE EYELID AND ADJACENT STRUCTURES: SHOULD THEY BE REMOVED? Crawford, J. S. (Dept. Ophthalmol., Hosp. for Sick Children, Toronto, Ontario, Can.). J. Pediatr. Ophthalmol. Strabismus 16:246, 1979.

Removal of lipodermoid tumors from the outer canthal region was complicated in four patients by blepharoptosis and in two by strabismus. Removal of lymphangioma and hemangioma of the eyelid has also resulted in blepharoptosis. Enlarged lacrimal gland has been mistaken for a tumor and removal was followed by a dry eye. Hemangiomas of the eyelid may cause astigmatism and amblyopia and must be treated when necessary. Deep resection of limbal dermoids has resulted in a filtering wound and may require a lamellar graft to prevent this. All these complications can occur with benign tumors which indicates that they should be treated with great care. (8 figures, 5 references)—Paul E. Romano

CONSERVATIVE MANAGEMENT OF CONGENITAL AMNIOTOCELE OF THE NASOLACRIMAL SAC. Levy, N. S. (Florida Ophthalmic Inst., Gainesville, and the VA Medical Ctr., Lake City, Fla.). J. Pediatr. Ophthalmol. Strabismus 16:254, 1979.

A 10-day-old white male, the product of a normal gestation and delivery, was found to have swelling in the area of the lacrimal sac, bilaterally. There was epiphora, but no evidence of purulent discharge. Examination revealed nontender, nonerythematous swelling of the sac. There was no reflux on compression. Diagnostic aspiration of the left sac revealed a sterile xanthochromic, non-purulent fluid. The diagnosis of congenital amniotocele of the lacrimal sac was made. Conservative management of warm compresses and massage was undertaken. Within ten weeks the problem resolved, bilaterally. This entity should be distinguished from the common dacryocystitis resulting from obstruction of the distal end of the nasolacrimal duct. Probing of the nasolacrimal system may

not be necessary in the treatment of uncomplicated congenital amniotocele of the lacrimal sac. (3 figures, 7 references)—Author's abstract

Klinische Monatsblaetter für Augenheilkunde

THE HISTOLOGY OF THE EXTRAOCULAR MUSCLE THICKENING SEEN IN DYSTHYROID ORBITOPATHY. (German) Daicker, B. (Univ. Eye Clinic, Basel, Switzerland). Klin. Monatsbl. Augenheilkd. 184:843, 1979.

A very constant characteristic of thyroid ophthalmopathy is thickening of the extraocular muscles. Five orbits from three patients with thyroid ophthalmopathy of one to nine years' duration were studied post mortem. The changes seen in the extraocular muscles included deposition of an acid mucopolysaccharide between the muscle fibers, and fibrosis. The mucopolysaccharide deposition seemed to account for the muscle enlargement. Lymphocytic infiltrate was mild and insufficient to cause muscle enlargement; mast cells were not found. One case had the unexpected finding of mature fat cells infiltrating the extraocular muscle. (8 figures, 18 references)—Peter Egbert

Lancet

MITRAL-ANNULUS CALCIFICATION AND CEREBRAL OR RETINAL ISCHEMIA. DeBono, D. P., and Warlow, C. P. (Depts. Cardiovascular Med., and Clin. Neurol., Univ. Oxford, Radcliffe Infirm., Oxford, England). Lancet 2:383, 1979.

Radiological and echocardiographic evidence of extensive mitral-annulus calcification was present in eight patients (aged 64 to 78) from a series of 151 consecutive patients presenting with symptoms of retinal or cerebral ischemia but in none of 188 controls matched for age and sex. The mitral-annulus calcification syndrome appears to be significantly associated with cerebral emboli, particularly in the elderly. Echocardiography is a valuable noninvasive means of making the diagnosis and distinguishing the condition from others with similar physical signs. (1 figure, 1 table, 9 references)—Authors' abstract

Laryngoscope

ORBITAL-FACIAL COMPLICATIONS OF SINUSITIS IN CHILDREN. Fearon, B., Edmonds, B., and Bird, R. (Depts. Otolaryngol., Hosp. for Sick Children and Univ. Toronto, Toronto, Ont., Canada). Laryngoscope 89:947, 1979.

The authors reviewed 6,770 pediatric admissions for sinusitis. Of these, 159 had orbital-facial complications and 17 required orbital drainage. Two patients developed optic atrophy. Sinusitis in children under five years of age involves the maxillary or ethmoid sinuses. Access to the orbit is by way of congenital bony dehiscences or suture lines and common venous channels. In newborns, staphylococcus is the most common offender. The authors' initial treatment of orbital cellulitis in the general pediatric group includes intravenous ampicillin, topical intranasal vasoconstrictors and oral decongestants. Persistence of eye signs may indicate an orbital abscess requiring surgical drainage. Other complications encountered were osteomyelitis, mucocele, cavernous sinus thrombosis, and meningitis. (1 figure, 5 references)—Gerald J. Harris

Neurology

ISOLATED BILATERAL OCULOMOTOR PARESIS DUE TO LYMPHOMA. Wilkins, D. E., and Samhouri, A. M. (Depts. Neurol. and Internal Med., Henry Ford Hosp., Detroit, Mich.). Neurology 29:1425, 1979.

Isolated bilateral third nerve palsies are an unusual presenting feature of neurologic disease. The likelihood of encountering this clinical picture is even more remote when the pupils are spared. A 62-year-old man with known histiocytic lymphoma was being treated with various chemotherapeutic agents. Over a four-week period he developed bilateral blepharoptosis and involvement of the extraocular muscles innervated by the third nerve. However, the pupils were spared. Shortly after this he died of a pulmonary embolus and postmortem

examination revealed lymphomatous infiltration of both ocular motor nerves. This is apparently the first patient with lymphoma to manifest these isolated findings. Sparing of the pupils can only be explained by the fact that the infiltrates were patchy rather than solid and contiguous. (2 figures, 9 references)—David Shoch

Proceedings of the National Academy of Sciences of the United States of America

LIGHT-INDUCED DAMAGE TO OCULAR LENS CATION PUMP: PREVENTION BY VITAMIN C. Varma, S. D., Kumar, S., and Richards, R. D. (Dept. Ophthalmol., Univ. Maryland Med. School, Baltimore, Md.). Proc. Natl. Acad. Sci. USA 76:3504, 1979.

The level of ascorbic acid in the lens and aqueous of many animals is much higher than it is in the blood and other body fluids. There has been no explanation for this unusual concentration of ascorbic acid in these structures. The authors offer the first explanation for this high concentration of vitamin C in the lens. It has been known that in tissues transparent to light a photochemical reaction can take place which is a conversion of normal oxygen to a superoxide by the addition of an electron. This superoxide is dismuted to hydrogen peroxide and the hydroxyl ion all of which would be injurious to the integrity of cell membranes unless the surrounding humoral fluids had appropriate scanvengers. The authors postulate that it is the ascorbic acid in high concentrations in the lens that performs this function and thus prevents light induced damage to the ocular lens. Further support for this theory might be the fact that vitamin C is not present in high concentration in the lenses of nocturnal animals who are not exposed to light. (1 figure, 27 references)—David Shoch

WHO Chronicle

DATA ON BLINDNESS THROUGHOUT THE WORLD. WHO Chron. 33:275, 1979.

Because the criteria for blindness vary from country to country it is not possible to get an exact figure but it is estimated there are between 28 million and 42 million blind people in the world today. The cause of blindness varies enormously but is obviously higher in countries underserved medically. For example, trachoma in areas of severe endemicity, may cause a rate of blindness of one to three percent. In areas heavily infected by onchocerciasis blindness rates of three to seven percent exist. Where malnutrition is an important cause of blindness, xerophthalmia/keratomalacia will be a leading cause; for example, it is estimated that there are 250,000 blind people in India from xerophthalmia/keratomalacia. On the other hand, in the same areas, cataract is a much more common cause of blindness and in India again, there are an estimated 3.5 million cases of blindness (visual acuity less than 3/60) caused by cataract. In the United States, on the other hand, according to a study done in 1970 from a model reporting area, retinal disease accounted for 25% of blindness, cataracts for 13%, glaucoma for 11%, optic nerve disease for 9%, uveitis for 5%, cornea and sclera for 4.7% and myopia for 3%. (2 tables, 31 references)—David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

Send News Items double-spaced to News Editor, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

TERTIUM FORUM OPHTHALMOLOGICUM

The Teritum Forum Ophthalmologicum will be held March 17-21, 1980 in Bogota, Columbia. The subjects to be covered include the following: Surgery of the Anterior Segment (a) Cornea; (b) Lens; (c) Glaucoma, Strabismus - Surgery of Hyperconvergence, Retinal Detachment and Vitreous, and Oculoplastic Surgery. For further information, write Dr. Zoilo Cuellar-Montoya, General Secretary, Apartado Aereo 90404, Bogota (8), Colombia.

UNIVERSITY OF LONDON— INSTITUTE OF OPHTHALMOLOGY: FIRST FOUNDATION LECTURE

Frank W. Newell gave the First Foundation Lecture, at the Institute of Ophthalmology, University of London, Nov. 28, 1979. The Foundation Lecture was established to pay tribute to the late Sir Stewart Duke-Elder. Dr. Newell spoke on "Medical education and scientific research in the decade to come."

NEW YORK MEDICAL COLLEGE: SEMI-ANNUAL OCULOPLASTIC SURGICAL DISSECTION COURSE

The semi-annual oculoplastic surgical dissection course will be held at the New York Medical College, Westchester County Medical Center, May 14-17, 1980. The fee is $600. For further information, write Ms. P. Tamkin, c/o Dr. P. Guibor, 630 Park Ave., New York, NY 10021.

NEW YORK MEDICAL COLLEGE: ANNUAL COSMETIC FACIAL SURGICAL DISSECTION COURSE

The annual cosmetic facial surgical dissection course will be held at the New York Medical College, Westchester County Medical Center, May 17-22, 1980. The fee is $800. For further information, write Ms. P. Tamkin, c/o Dr. P. Guibor, 630 Park Ave., New York, NY 10021.

UNIVERSITY OF TEXAS MEDICAL SCHOOL: OCULOPLASTIC SURGERY SYMPOSIUM

The University of Texas Medical School will sponsor an Oculoplastic Surgery Symposium, June 29-July 3, 1980. The registration fee is $375. A deposit of $250 per room is required. For further information, write Robert B. Wilkins, M.D., 1100 Hermann Professional Bldg., Houston, TX 77030.

AZAR FOUNDATION: FIFTH ANNUAL NEW ORLEANS SPRING FIESTA OPHTHALMOLOGY SEMINAR

The Fifth Annual New Orleans Spring Fiesta Ophthalmology Seminar will be held May 21-24, 1980. Subjects of the meeting include intraocular implants, intracapsular and extracapsular cataract techniques, refractive keratoplasty, extended-wear contact lenses, cosmetic surgery of the aging eye, corneal and vitreous surgery. For further information, write the Azar Foundation, 144 Elk Place, Suite 1501, New Orleans, LA 70112.

GEORGETOWN UNIVERSITY CENTER FOR SIGHT: TWO-YEAR TRAINING PROGRAM FOR OPHTHALMIC TECHNICIANS

Georgetown University for Sight offers a two-year training program for ophthalmic technicians June 23, 1980 - June 30, 1982. Tuition is $1,800 a year. The application deadline is May 1, 1980. For further information, write Ms. Candace P. Wolfe, Director, Ophthalmic Technician Program, Georgetown University, Center for Sight, 3800 Reservoir Rd., N. W., Washington, DC 20007.

GEORGETOWN UNIVERSITY CENTER FOR SIGHT: TEN-WEEK COURSE FOR OPHTHALMIC ASSISTANTS

Georgetown University Center for Sight will offer a ten-week course for ophthalmic assistants June 23 - Aug. 29, 1980. Tuition is $250. Application deadline is June 1, 1980. For further information, write Ms. Candace P. Wolfe, C.O.T., Director, Ophthalmic Technician Program, Georgetown University Medical Center, Center for Sight, 3800 Reservoir Rd., N. W., Washington, DC 20007.

FIFTY-THIRD ANNUAL NEW YORK EYE AND EAR INFIRMARY CLINICAL CONFERENCE

The 53rd Annual New York Eye and Ear Infirmary Clinical Conference, "Ophthalmology 1980," will be

held May 8 and 9, 1980, in New York City. For further information, write Ms. Jane Stark, Conference Registrar, New York Eye and Ear Infirmary, 310 E. 14th St., New York, NY 10003.

Society of Air Force Clinical Surgeons: Surgical Postgraduate Seminar

The Society of Air Force Clinical Surgeons will sponsor a surgical postgraduate seminar April 13-16, 1980, at the Convention Center of the Four Seasons Motor Inn, Colorado Springs, Colorado. For further information, write Colonel Clint E. Chambers, Chairperson, Dept. of Surgery, USAF Medical Center/SGHS, Wright-Patterson AFB, OH 45433.

Ophthalmology Update Course

The second two-year cycle of the Update Course in Ophthalmology will begin on March 7 and 8, 1980. The course will be given on a Friday and Saturday every three months for a two-year period. It is co-sponsored by the University of California, Davis; Pacific Medical Center, University of California, San Francisco; and Stanford University. For further information, write Update, 3910 Sand Hill Road, Woodside, CA 94062.

Asociación Para Evitar La Ceguera: Ocutome/Fragmatome Workshop and Course

The Asociación para Evitar la Ceguera will hold an Ocutome/Fragmatome Workshop May 14-15, 1980, and a course May 16-17, 1980, at its hospital in Mexico City. For further information, write Raúl Santos, M.D., Course Director, Aristóteles 98, México 5, D. F., Mexico.

Doctor-To-Doctor Medical Journal Program

Doctors in the United States are asked to send their medical journals-after having read them-to colleagues overseas (Asia, Latin America, and Africa) who wish to have access to current medical literature but because of either currency regulations or actual costs involved, cannot themselves subscribe to medical periodicals. Participants will be supplied with the name, address, and medical speciality of doctors, in these areas who wish to receive much-wanted journals (particularly specialty journals) and will mail them directly, to their overseas colleague. The "Doctor-to-Doctor" program is sponsored by the American Medical Association with the collaboration of the World Medical Association. Persons wishing to participate in the program should send their names, addresses, and title of journals they would be willing to contribute to Doctor-to-Doctor Program, c/o The World Medical Association, Inc., 10 Columbus Circle, New York, NY 10019.

Ophthalmology and Otorhinolaryngology Society Meeting

The University of Texas Health Science Center at San Antonio will sponsor the Ophthalmology and Otorhinolaryngology Society meeting, Feb. 23, 1980. For further information, write Office of Continuing Education Services, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78284.

Personals

Barton L. Hodes

Barton L. Hodes has been named Professor and Head, Division of Ophthalmology, Milton S. Hershey Medical Center, Hershey, Pennsylvania.

William F. Hughes

William F. Hughes presented the Third James E. McDonald Lecture Oct. 19 at the Eye Department of Loyola Medical School. His topic was "A Potpourri of Classical Articles Gleaned from 20 Years of the Year Book of Ophthalmology."

Richard S. Ruiz

Richard S. Ruiz has been named chairman, Department of Ophthalmology, University of Texas Health Science Center, Houston, Texas.

William S. Tasman

William S. Tasman has been named chairman, Department of Ophthalmology, Medical College of Pennsylvania, Philadelphia, Pennsylvania.

New Research Grants Awarded By The National Eye Institute
July 1, 1979, to September 30, 1979

Research Project Grants

Institution	Principal Investigator	Title of Project	Amount Awarded
Eye Research Institute of Retina Foundation Boston, Massachusetts	Alice J. Adler	Biochemical aspects of retinal adhesion	$ 65,049
University of Wisconsin Madison, Wisconsin	Robert Auerbach	Angiogenesis in the mouse eye	78,292
Emory University Atlanta, Georgia	Joseph C. Besharse	Visual cell - Pigment cell interface and disc turnover	98,724
Harvard University Cambridge, Massachusetts	Paul K. Brown	Microspectrophotometry of photoreceptors	120,409
University of Washington Seattle, Washington	Steven L. Buck	Interaction in the visual system	50,090
Emory University Atlanta, Georgia	David G. Campbell	Pigmentary glaucoma therapy: Thymoxamine, macrophages	120,812
University of Wisconsin Madison, Wisconsin	Suresh R. Chandra	Macular photo-coagulation study	37,368
Oxford Area Health Authority Oxford, United Kingdom	Hung Cheng	Cataract management—a randomized controlled trial	127,335
University of California La Jolla, California	Patrick H. Cleveland	Immunodiagnosis of ocular herpes virus infections	65,132
American Registry of Pathology Washington, District of Columbia	Ben S. Fine	Foveomacular aging in the rhesus monkey	106,885
Massachusetts General Hospital Boston, Massachusetts	Warren E. Foote	Studies of retinal afferents to the brain stem raphe	78,014
Jackson Laboratory Bar Harbor, Maine	Richard R. Fox	Pathogenesis of glaucoma—like changes in buphthalmos	99,383
University of California Berkeley, California	Ralph D. Freeman	Spatial adaptation of neurons in striate cortex	37,988
University of Washington Seattle, Washington	Albert F. Fuchs	Neuroanatomy of the oculomotor system	53,500
Cornell University Ithaca, New York	Lawrence T. Glickman	Toxocara infection and ocular disease	108,911

Institution	Principal Investigator	Title of Project	Amount Awarded
Yale University New Haven, Connecticut	Timothy H. Goldsmith	Avian color vision	$ 33,831
Case Western Reserve University Cleveland, Ohio	Bruce M. Greene	Onchocerciasis: Immunologically-mediated eye disease	127,145
Ohio State University Columbus, Ohio	Carl R. Ingling, Jr.	The color and brightness channels of the visual system	44,341
University of Tennessee Center Health Sciences	Howard M. Jernigan	Nitrogen metabolism in the crystalline lens	45,729
Harvard University Boston, Massachusetts	Pamela A. Johns	Neurogenesis and synaptogenesis of retinal photoreceptor	76,594
University of Southern California Los Angeles, California	Douglas E. Kelly	Fine structure of uveal barriers to intraocular fluid	60,359
Stanford, University Stanford, California	Joseph P. Kriss	Cell-mediated cytotoxicity in Graves' ophthalmology	98,758
Columbia University New York, New York	Francis A. L'Esperance, Jr.	Intraocular tumor vaporization by CO_2 laser radiation	93,613
Gothenburg University Gothenburg, Sweden	Erik E. Linner	Prospective study of ocular hypertensive subjects	50,875
Medical University of South Carolina Charleston, South Carolina	Jennifer S. Lund	Structural basis for processing visual information	154,289
University of Oklahoma Health Science Center Oklahoma City, Oklahoma	Wayne F. March	Macular photocoagulation study	58,776
William Beaumont Hospital Royal Oak, Michigan	Raymond R. Margherio	Macular photocoagulation study	53,699
Rush University Chicago, Illinois	Richard T. Mathias	Volume regulation in normal and cataractous lenses	66,250
Yale University New Haven, Connecticut	William H. Miller	Photoreceptor function	88,709
Ingalls Memorial Hospital Harvey, Illinois	David H. Orth	Macular photocoagulation study	40,844
Yale University New Haven, Connecticut	David S. Papermaster	Immunocytochemistry of membrane biosynthesis in eye	107,965
University of Virginia Charlottesville, Virginia	Elsa P. Paulsen	Retinal/renal capillary leakage in childhood diabetes	113,655

Institution	Principal Investigator	Title of Project	Amount Awarded
Dalhousie University Halifax, Canada	David Regan	Psychophysical and EP assessment of visual pathology	$106,705
Brown University Providence, Rhode Island	Lorrin A. Riggs	Visual significance of eye blinks	58,444
Children's Hospital Medical Center Boston, Massachusetts	Richard L. Sidman	Optic nerve axon growth in mouse pigmentation mutants	99,703
St. Luke's Hospital United Methodist Church Cleveland, Ohio	Lawrence J. Singerman	Macular photocoagulation study	29,377
Estelle Doheny Eye Foundation Los Angeles, California	Nino Sorgente	Vitreo-retinal control of vascular proliferation	127,226
University of Texas Health Science Center Houston, Texas	Harry G. Sperling	Light hazards in ophthalmic diagnosis and treatment	23,350
University of Texas Health Science Center Dallas, Texas	Richard Srebro	Pseudorandom stimuli for clinical VEP testing	117,631
Eye Research Institute of Retina Foundation Boston, Massachusetts	Richard A. Thoft	Effects of diabetes mellitus on ocular surface	33,588
University of Illinois Medical Center Chicago, Illinois	Rockefeller S. Young	Psychophysical study of photopic abnormalities	83,694
Massachusetts Eye and Ear Infirmary Boston, Massachusetts	Johan Zwaan	Genetic controls in eye lens development	140,571

Core Center Grants

Institution	Principal Investigator	Project Title	Amount Awarded
University of Alabama Birmingham, Alabama	Terry L. Hickey	Vision research center (core)	$307,756
Estelle Doheny Eye Foundation Los Angeles, California	Stephen J. Ryan	Visual science research support	312,404

National Research Service Award Fellowships

Institution	Principal Investigator	Project Title	Amount Awarded
Baylor College of Medicine Houston, Texas	Lary D. Andrews	Age-related chemical and morphological changes in retina	$ 13,200

Institution	Principal Investigator	Title of Project	Amount Awarded
University of Colorado Boulder, Colorado	Steven M. Archer	Role of action potentials in visual system maturation	$ 13,800
New York University New York, New York	Aries R. Arditi	Binocular combination in striate cortex	13,000
University of Virginia Charlottesville, Virginia	G. Bea Aton	Structure function relationships in rhodopsin membrane	15,200
Brown University Providence, Rhode Island	David M. Berson	Visual integration in the superior colliculus	13,000
Yale University New Haven, Connecticut	Michael H. Chaitin	Immuno-affinity partitioning of retinal membranes	13,000
Stanford University Stanford, California	Charles E. Cima	Morphogenesis of astrocytes in the anuran optic nerve	13,000
Stanford University Stanford, California	John W. Crabtree	Altered CNS activity and visuocortical development	14,500
University of California San Francisco, California	Edwin R. Griff	Pigment epithelial interactions with the neural retina	13,000
University of Pennsylvania Philadelphia, Pennsylvania	James E. Hamons	Visual cortex micro-circuitry: glycine and gaba neurons	13,000
University of Pennsylvania Philadelphia, Pennsylvania	Susan J. Herdman	Recovery of visual responses in primates	14,900
Syracuse University Syracuse, New York	Leonard J. Kass	Efferent control of retinal sensitivity	13,000
Northwestern University Evanston, Illinois	Lawrence E. LeGuire	Psychophysical investigators into strabismus	13,000
University of California Santa Cruz, California	James W. Lewis	Photochemistry of visual pigments	14,500
Medical University of South Carolina Charleston, South Carolina	Linda K. Mc Loon	Antigenic changes in the developing visual system	13,000
University of New South Wales Kensington, Australia	David H. Rapaport	Morphology physiology and projections of monkey retina	12,000
U.S. National Institutes of Health Bethesda, Maryland	David H. Rohrback	The composition and construction of basement membrane	10,000
University of Washington Seattle, Washington	James A. Stevenson	Plasticity among tectal efferents	13,000

Institution	Principal Investigator	Title of Project	Amount Awarded
University of Illinois Medical Center Chicago, Illinois	Carol S. West	Retinal disease: a study of two canine models	$ 15,800

Research Career Development Awards/Academic Investigator Awards

Institution	Principal Investigator	Project Title	Amount Awarded
Emory University Atlanta, Georgia	Joseph C. Besharse	The visual cell - pigment cell complex and outer segment	$ 28,831
New York University New York, New York	Ardith Y. Bondi	Electophysiology of oculomotor muscles	26,713
Louisiana State University Medical Center New Orleans, Louisiana	Thomas J. Zimmerman	Treatment of glaucoma	35,802

Institutional National Research Service Awards

Institution	Principal Investigator	Project Title	Amount Awarded
Colorado State University	Eugene L. Pautler	Ophthalmology	$ 35,112

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3. Duke-Elder, S., and Leigh, A. G.: Diseases of the Outer Eye. Cornea and Sclera. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 8, pt. 2. St. Louis, C. V. Mosby, 1965, pp. 811-856.

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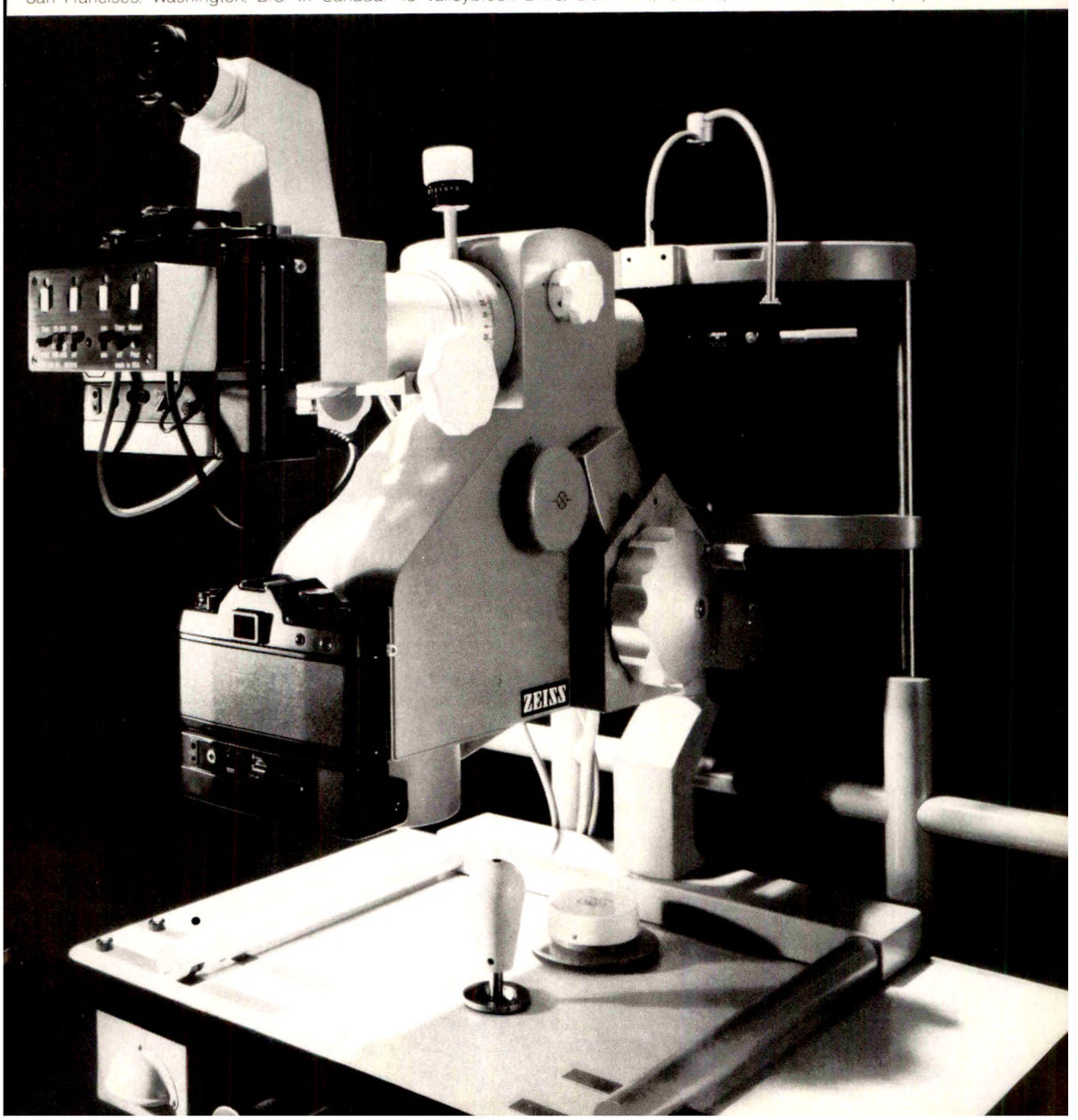

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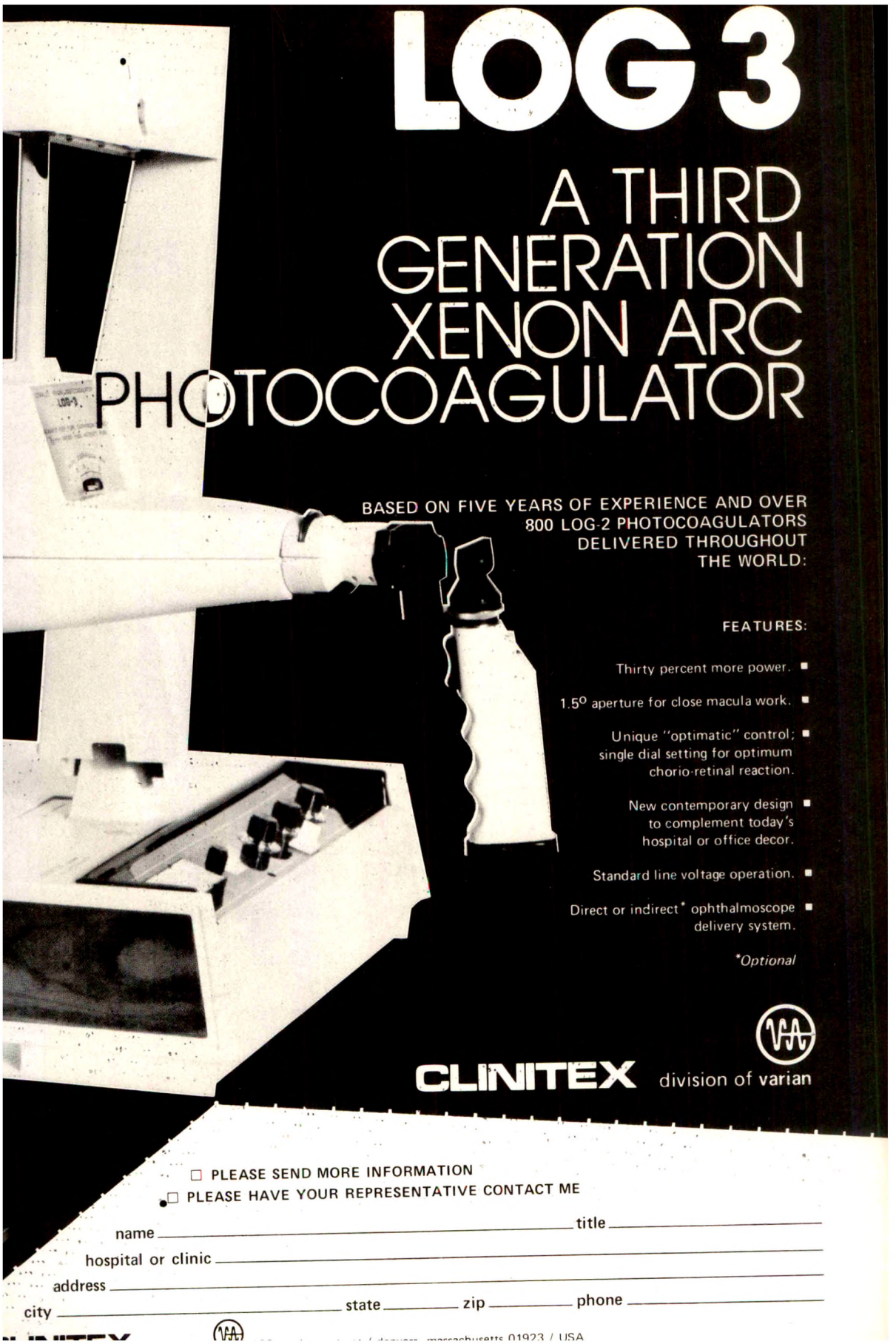

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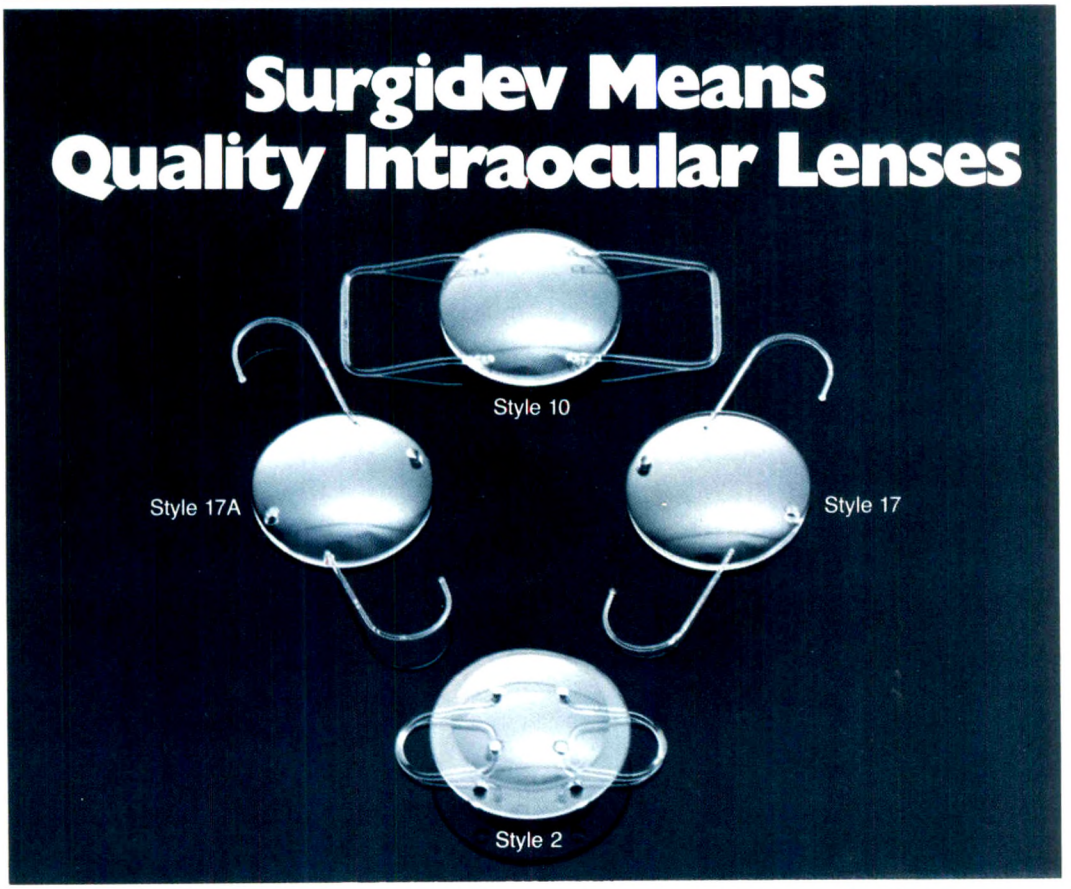

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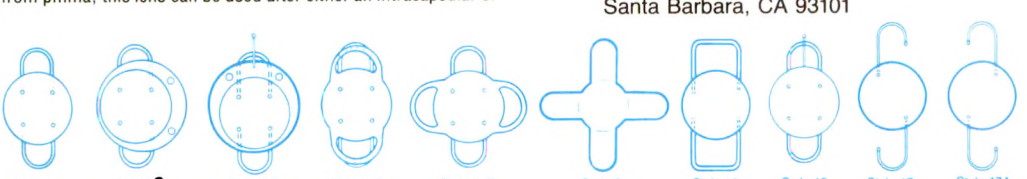

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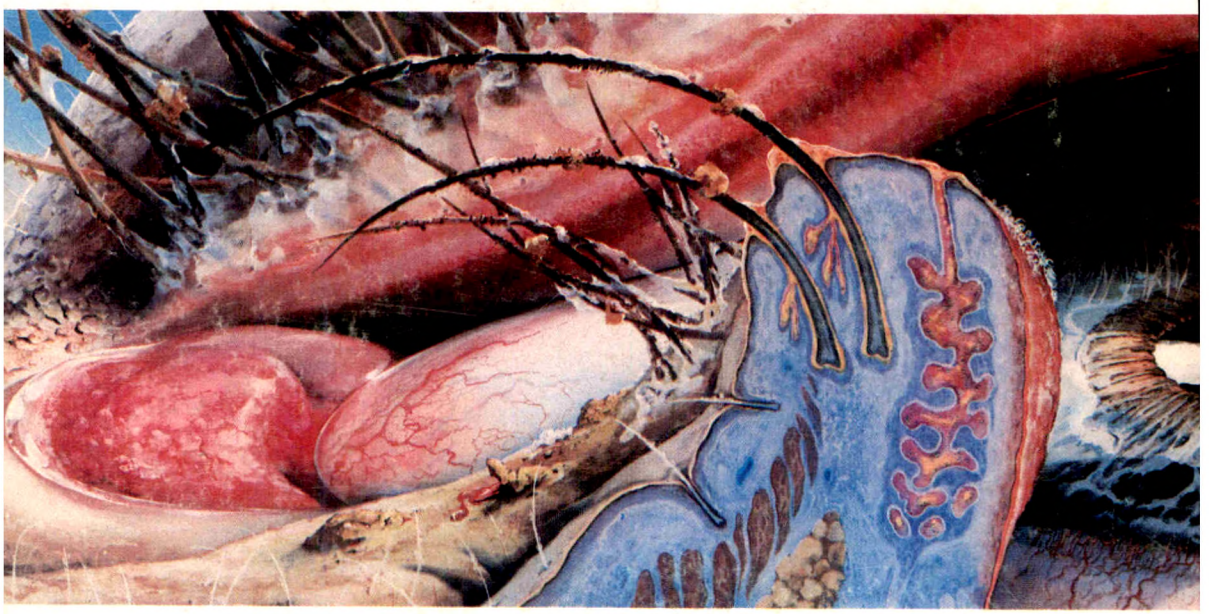

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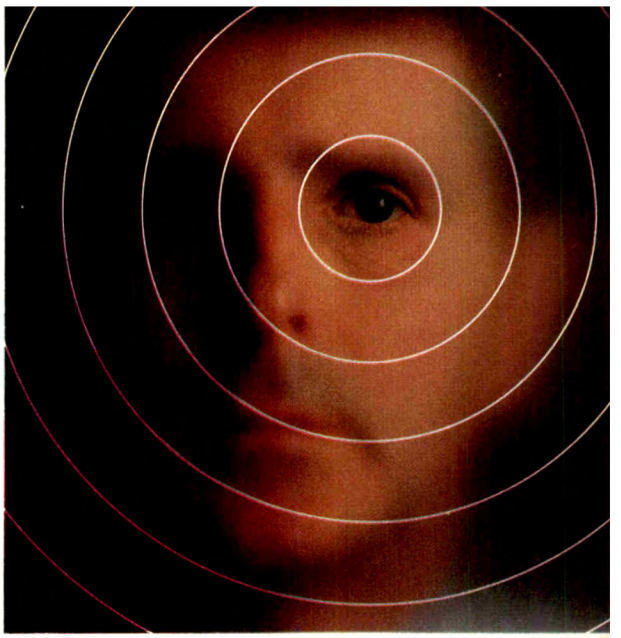

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Boger WP: Timolol: Short Term "Escape" and Long Term "Drift" ANN OPHTH 11:8(1239) 1979.
Thomas JV, Epstein DL: Transient Additive Effect of Timolol and Epinephrine in Primary Open-Angle Glaucoma: Glaucoma Clinical Research Center, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston Mass.
Fraunfelder FT et al: Research Leads to More Effective Ways of Administering Eyedrops JAMA 236: 21 Nov 22 1978.

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2. Marun, Edgard. Evaluation of a new topical steroid. Fluorometholone, in the postoperative course of the cataract operation. Ann Ophthalmol 7:139-142, 1975.

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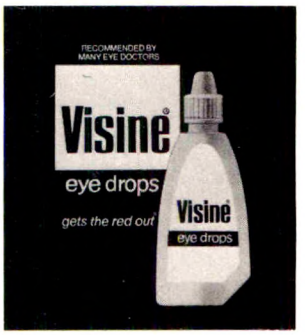
Applications are invited for a National Eye Institute training fellowship in experimental ophthalmic pathology, starting 1 July 1980. The fellowship program runs for two years. Emphasis is placed on acquiring skills in the performance of experimental ocular pathology. Concurrently, a broad understanding of ophthalmic pathology is fostered. All facilities at the Scheie Eye Institute, the Presbyterian-University of Pennsylvania Medical Center and the University of Pennsylvania are available for training and learning of specialized research skills. Those interested should direct inquiries, and send an up-to-date curriculum vitae and bibliography to:

Myron Yanoff, M.D.
Director, Scheie Eye Institute
Chairman, Department of Ophthalmology
University of Pennsylvania-
Presbyterian Medical Center
51 North 39th Street
Philadelphia, PA 19104

(Tetrahydrozoline HCl) ...an excellent vasoconstrictor among ophthalmic solutions



Dispensing Information

Composition: Tetrahydrozoline hydrochloride 0.05%; sodium chloride; boric acid; sodium borate; with benzalkonium chloride 0.01% and disodium ethylene diamine tetraacetate 0.1% added as preservatives.

Uses: For fast, lasting relief from minor irritation of eyes due to Dust-Smoke-Smog-Contact Lens adaptation (after removal of lenses).

Plant Allergies such as hay fever and rose fever. Minor eye irritation from or due to night driving, reading, T.V., sewing, swimming, wind and sun glare.

Refreshes, soothes and helps relieve redness caused by minor irritations.

Warning: Use only in the eyes. If relief is not obtained within 48 hours, or if irritation or redness persists or increases, discontinue use and consult your physician. Infection, pus, draining, foreign body in the eye, any mechanical, chemical, heat or other injury to the eye require the immediate attention of your physician. As with other eye medications, Visine should not be used by individuals with glaucoma or other serious eye diseases.

Parents: Keep this and all other medications out of the reach of children. Before using with children, consult your physician.

Directions: Place 1 or 2 drops in each eye two or three times a day as directed by physician. Visine is produced under sterile conditions.

Visine® professional samples on request

To receive free samples (twenty-four ¼-oz. Visine samples) for your patients, just fill out the coupon below: AJO 2-80

Name _____
Please print

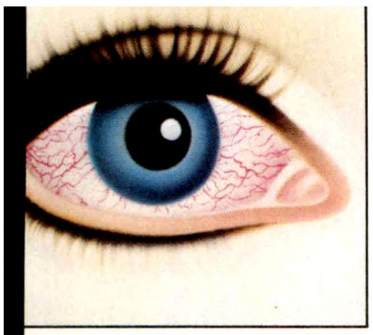
Address _____

City _____

State _____

Zip _____

Mail to: Visine Redemption Center
Leeming Division, Pfizer Inc.
100 Jefferson Road, Parsippany, NJ 07054

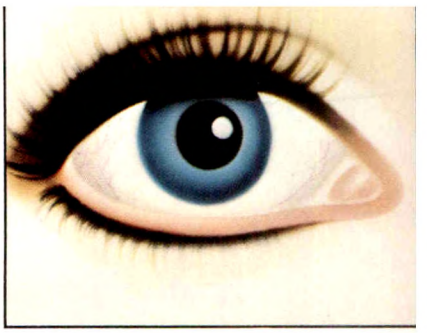


e problem:

to relieve hyperemia caused inor eye irritation.

The treatment:

Recommend Visine® (Tetrahydrozoline HCl), a safe and effective treatment used in millions of cases of minor eye irritation.



The relief:

With Visine® the onset of vasoconstriction is rapid—the resulting decongestion dramatic.

sine® (Tetrahydrozoline HCl) . . . n excellent vasoconstrictor mong ophthalmic solutions.

esults seemed to indicate that – Tetra-drozoline Hydrochloride – is an excellent phthalmic decongestant..."

ossmann and Lehman—
erican Journal of Ophthalmology, 42 #1, 121-123, July 1, 1956.

ffectively relieves ocular ongestion with a low incidence f undesirable side effects.

After the effects of vasoconstriction had sub-ded the eyes did not become more red than reviously, indicating the absence of rebound asodilation."

ossmann and Lehman—
nerican Journal of Ophthalmology, 42 #1, 121-123, July 1, 1956.

here was complete absence of undesirable de effects...No untoward changes occurred the conjunctiva or other ocular tissues re-ardless of the length of time tetrahydrozoline as used."

I. Stokes—Journal of A.M.A. Georgia, 340-341, November 1958.

In addition to its excellent decongestant ction, which provided prompt symptomatic elief, an important feature of Tetrahydrozoline ydrochloride) is its low incidence of side ef-ects...limited to a mild stinging sensation in 1% of the patients."

C. Menger—Journal of A.M.A., Vol. 170, 178-179, May 1959.

Further confirmation of Visine's safety is rovided by the low number of adverse reac-on complaints received. In each of the last five years, such complaints have averaged fewer than 2 out of every million bottles sold.

Quickly provides effective decongestant action to bring lasting relief.

A double-blind test conducted among 100 patients indicated that 87 patients had hyperemia-free eyes in 5 minutes or less—59 of them in 1 minute or less. Other tests suggest a prolonged duration of effect unaccompanied by rebound hyperemia.

Double-blind evaluation of Visine—relief of symptoms of eye fatigue and irritation. Study #0152-8/72, February 1973.

Ideal isotonic formulation provides maximum comfort by maintaining normal hydration and thickness of cornea.

Visine ophthalmic solution—with a tonicity of about 290 mOsm/kg – matches that of 0.9 percent sodium chloride solution which is normal for tears. Thus Visine is formulated to avoid adversely affecting proper corneal thickness or causing discomfort.

Proper combination of both pH and buffering capacity assures comfortable instillation.

Visine ophthalmic solution has been formulated to have a pH of 6.2-6.5 and a low buffering capacity. This combination provides better stability of Tetrahydrozoline HCl and minimizes stinging and irritation by allowing the product to attain the normal pH of tears (7.4) very quickly after instillation into the eye.

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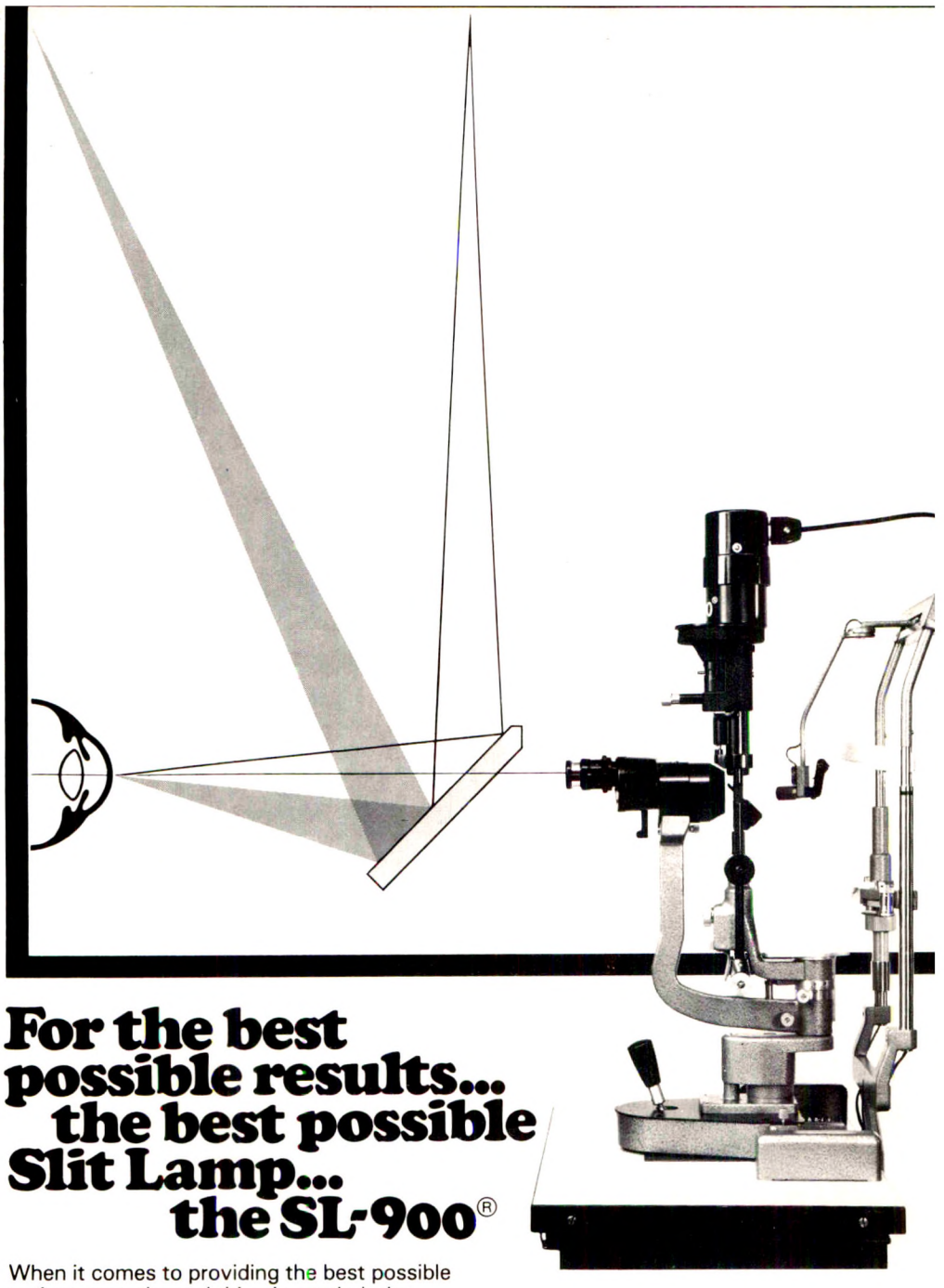

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When it comes to providing the best possible patient care, the real thing is needed, the best possible Slit Lamp... the SL-900® by Haag-Streit. To experience optical resolution as it really should be... to observe details with the truly finest slit system... and to arrive at an unquestionably assured diagnosis, rely on the original. The finest skills can only be excercised with the finest instruments. Such instruments cost more because they do more. Over 10,000 U.S. Haag-Streit SL-900® users know what this means. If you don't, move up now to the original. Contact us for full details on the SL-900® and a free copy of Haag-Streit's book, «On Slit Lamp Microscopy», or get in touch with your local Haag-Streit distributor.

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Subsidiary of Haag-Streit AG., Berne, Switz
6 Industrial Park, Waldwick, New Jersey 07
(201) 445-1110

The Ocutome II/Fragmatome II System opens a new world of precision.

The name synonymous with superior intraocular surgical equipment is Ocutome® /Fragmatome.™ It was the first microsurgical **system** to permit bimanual control and to feature the **smallest** (20-gauge) suction-cutter probe. Cooper Medical Devices now continues this tradition of setting standards through revolutionary designs, with the introduction of Ocutome® II/Fragmatome™ II.

Precision Footswitch Control
Working on a linear principle, the newly designed optional footswitch control delivers full-range suction capabilities in infinitely variable increments from 0 to a pre-set maximum (up to 300 mm Hg). Simple to operate, the two-pedal arrangement dovetails the functions of the Ocutome® II and the Fragmatome™ II. This allows the system to be used as an I/A instrument, a tissue suction/cutter or a lens fragmentation unit. Especially when suction can affect the outcome—as in cortical tissue removal prior to IOL insertion—the **Charles Linear Suction Footswitch Control** provides the required level of precise control for safe and successful manipulation.

Precision in Design and Function
From its functionally elegant exterior

to its highly responsive electronic circuitry, the system says **precision.** An optional built-in illumination module with fluorescein filter streamlines the system. Two suction valves allow concurrent attachment of the Ocutome® Probe and the improved Fragmatome™ Handpiece, making both ready for immediate use. The Console's lighted panels (LEDs) simultaneously display the pre-set maximum and actual suction levels in metric units. The cutting speed is fully variable from 60 to 480 cuts/minute. Other features bring added convenience. For quick availability, many of the procedure-related items are contained in sterile, pre-packaged Disposa-Kits.™ This, together with a new probe sterilization tray (which allows accessories to be wrapped and stored sterile), means that the unit is always ready for immediate emergency use. The Disposa-Bottle™ collection system also facilitates sterile tissue sampling and features a shut-off float to prevent bottle overflow.

Precisely The Same Features
The features of the Ocutome® / Fragmatome™ System—that put it light-years ahead of anything in its field and made it **the choice** for anterior-segment surgery—have not been changed. Yet the redesigned features add immensely to the system's flexibility, convenience and precision in procedures such as **capsulectomies, anterior vitrectomies, pupillary reshaping** and **retro-IOL membrane removal.** Of course, our commitment to **total** support through technical and educational services and ongoing R&D remains constant.

For more information on the Ocutome® II/Fragmatome™ II System or to receive our newsletter or workshop schedule, write us or call toll-free: (800) 227-0591; in California call (415) 568-6800.

Cooper Medical Devices
Berkeley Bio-Engineering
600 McCormick Street, San Leandro, CA 94577

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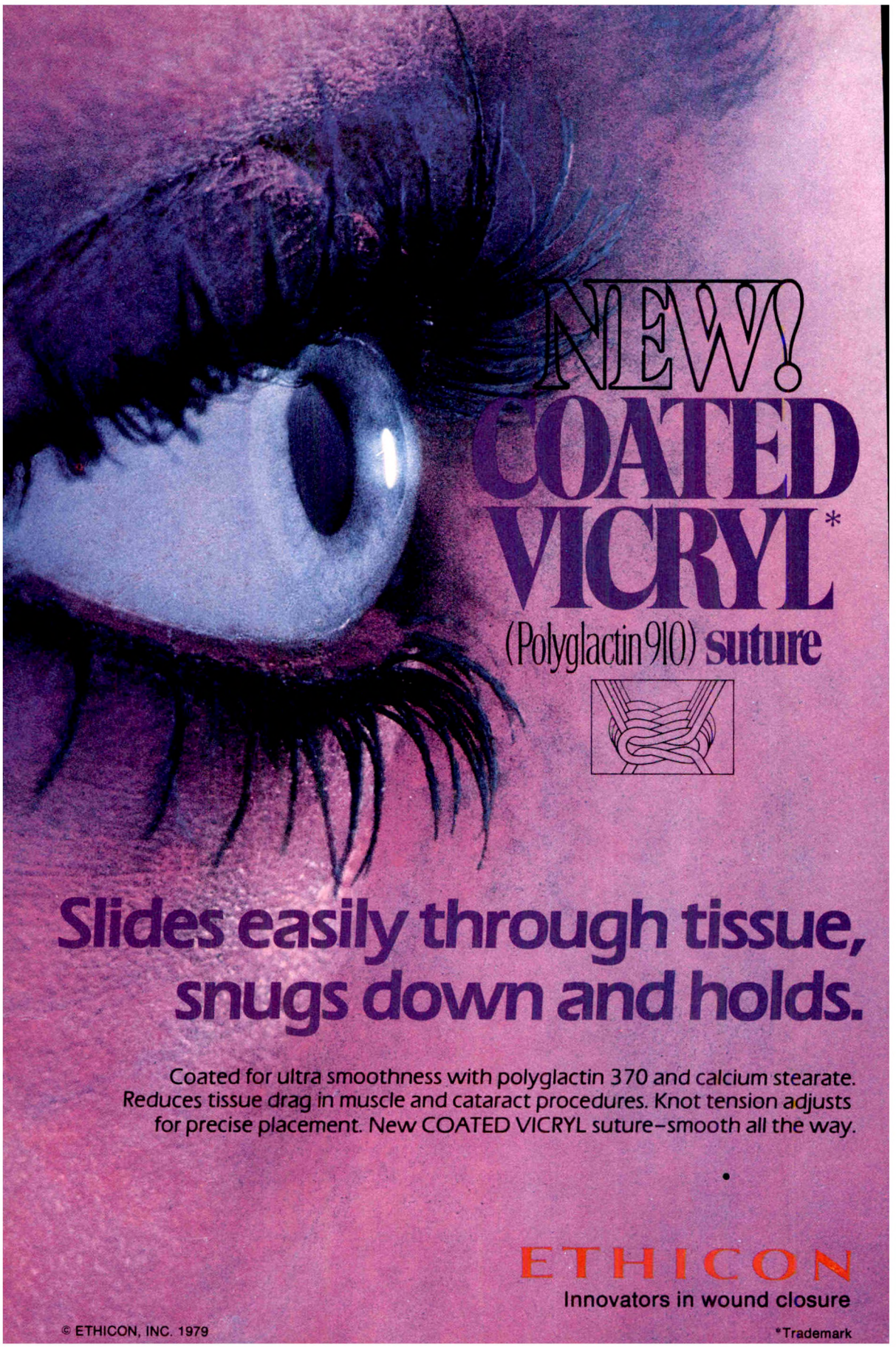
NEW!
COATED
VICRYL*
(Polyglactin 910) suture
Slides easily through tissue,
snugs down and holds.
Coated for ultra smoothness with polyglactin 370 and calcium stearate.
Reduces tissue drag in muscle and cataract procedures. Knot tension adjusts
for precise placement. New COATED VICRYL suture–smooth all the way.
ETHICON
Innovators in wound closure
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Revised: 3/79

VICRYL*
(Polyglactin 910) Suture
SYNTHETIC ABSORBABLE SUTURE

Coated VICRYL*
(Polyglactin 910) Suture
Coated with Polyglactin 370 and Calcium Stearate
SYNTHETIC ABSORBABLE SUTURE

DESCRIPTION
VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)_m(C_3H_4O_2)_n$.

Coated VICRYL synthetic absorbable suture is prepared by coating the VICRYL (polyglactin 910) suture material with a mixture composed of equal parts of a copolymer of glycolide and lactide (polyglactin 370) and calcium stearate.

These sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption. The braided and monofilament sutures are colored violet to enhance visibility in tissue. The braided suture is also available undyed (natural).

VICRYL and Coated VICRYL sutures differ from U.S.P. maximum diameter requirements by less than 0.05mm.

ACTIONS
Two important characteristics describe the *in vivo* behavior of absorbable sutures: first, tensile strength retention, and second, the absorption rate (loss of mass).

Subcutaneous tissue implantation studies of both VICRYL and Coated VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its orginal strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

INDICATIONS
VICRYL and Coated VICRYL synthetic absorbable sutures are intended for use as absorbable sutures or ligatures.

CONTRAINDICATIONS
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

WARNINGS
The safety and effectiveness of VICRYL (polyglactin 910) and Coated VICRYL sutures in neural tissue and in cardiovascular tissue have not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize.

PRECAUTIONS
The VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop; tie the second throw square, using horizontal tension; additional throws are advisable.

Coated VICRYL sutures, which are treated to enhance handling characteristics, require the standard surgical technique of flat and square ties with additional throws if indicated by surgical circumstance and the experience of the surgeon.

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

ADVERSE REACTIONS
Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration, rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses.

DOSAGE AND ADMINISTRATION
Use as required per surgical procedure.

HOW SUPPLIED
VICRYL sutures are available sterile as braided dyed (violet) strands in sizes 9-0 thru 3 (metric size 0.3—6) and undyed (natural) strands in sizes 8-0 thru 3 (metric size 0.4—6), in a variety of lengths, with or without needles, and on LIGAPAK® ligating reels. VICRYL sutures, monofilament, dyed (violet) are available in sizes 10-0 (metric size 0.2) and 9-0 (metric size 0.3), in a variety of lengths with needles.

Coated VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 8-0 thru 2 (metric size 0.4—5), in a variety of lengths, with or without needles, and on LIGAPAK ligating reels.

Both VICRYL and Coated VICRYL are also available in sizes 4-0 thru 1 (metric size 1.5—4) attached to ATRALEASE™ CONTROL RELEASE™ removable needles.

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Trademark

ETHICON

Announcement of the
Twentieth Annual Instructional Course In Contact Lens Fitting
Friday and Saturday, March 28-29, 1980
NEW ORLEANS
Sponsored by
The Rudolph Ellender Medical Foundation
In conjunction with
The Louisiana State University Eye Center
Endorsed by
The Contact Lens Association Of Ophthalmologists
A.M.A. —Approved as
Continuing Medical Education Program
(Sixteen Hours Credit in Category I)

PLACE: Fairmont Hotel, New Orleans

TUITION: $225.00 (Please make check payable to Rudolph Ellender Med. Fd. Mail to 136 S. Roman, New Orleans 70112 U.S.A.)

FACULTY:
JOS. A. BALDONE, M.D., New Orleans
OLIVER H. DABEZIES, JR., M.D. New Orleans
MILES H. FRIEDLANDER, M.D., New Orleans
RICHARD J. HESSE, M.D., New Orleans
FRANK B. HOEFLE, M.D., New York City
BREIN HOLDEN, PH.D., Kensington, Australia
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EDWARD L. SHAW, M.D., Phoenix, Arizona
TOM F. SPRING, M.D., Kew, Australia
LOUIS A. WILSON, M.D., Atlanta, Georgia

TOPICS: Conventional hard and soft contact lenses, and extended wear contact lenses.

Pre-Course Basic Lectures: 4 hours on the basics of hard and soft contact lens fittings on Thursday afternoon, March 27, 1980—Additional tuition $50.00

Basic Lectures: By Industry—no additional fee, Friday and Saturday evenings, March 28-29, 1980.

Post-Course Modification Seminar: Sunday, March 30, 1980—8:00 a.m. 'til 12 noon—Hard Lens Modification Course with audience participation—Limit 36 Persons—Additional tuition $50.00

FOR FURTHER INFORMATION CONTACT:

Jos. A. Baldone, M.D.
L.S.U. EYE CENTER
136 So. Roman
New Orleans 70112 U.S.A.
Ph: (504) 568-6839

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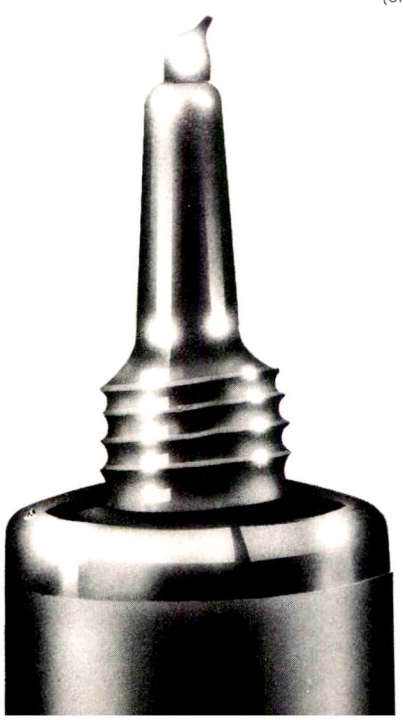
Usually French Quarter and Garden District Tour

Cortisporin® Ophthalmic Suspension
(Sterile)

For your eyes only!

Cortisporin® Ophthalmic Ointment
(Sterile)



☐ ***Because of your specialized knowledge and training,*** we believe that only you should prescribe the Cortisporin® ophthalmic products—and that's why they are promoted only to ophthalmologists.

☐ ***For your patients*** the Cortisporin ophthalmic products provide a wide therapeutic spectrum. The antibacterials act together against susceptible bacterial pathogens commonly involved in the ophthalmic infections accessible to topical therapy.* The hydrocortisone component gently and rapidly relieves signs and symptoms of inflammation and inhibits corneal neovascularization.

☐ ***Economical, too,*** with the two sterile forms providing convenient day and night coverage at lower cost than most other major brands of similar activity.

Cortisporin® Ophthalmic Suspension Sterile

(Polymyxin B–Neomycin–Hydrocortisone)

Each cc. contains: Aerosporin® brand Polymyxin B Sulfate, 10,000 Units; neomycin sulfate (equivalent to 3.5 mg. neomycin base), 5 mg.; hydrocortisone, 10 mg. (1%); thimerosal (preservative), 0.001%.
The vehicle contains the inactive ingredients cetyl alcohol, glyceryl monostearate, liquid petrolatum, polyoxyl 40 stearate, propylene glycol and purified water.

Cortisporin® Ophthalmic Ointment Sterile

(Polymyxin B–Bacitracin–Neomycin–Hydrocortisone)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; zinc bacitracin 400 Units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); hydrocortisone 10 mg (1%); special white petrolatum qs.

***INDICATIONS:** Based on a review of these drugs by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: For the treatment of nonpurulent bacterial infections of the eye due to organisms sensitive to the antibiotic ingredients of the drugs and when the anti-inflammatory action of the hydrocortisone is indicated as in nonpurulent bacterial, allergic, vernal and phlyctenular conjunctivitis; nonpurulent blepharitis; interstitial, sclerosing, postoperative or acne rosacea keratitis; superficial chemical and thermal burns of the cornea.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: These products are contraindicated in acute purulent conjunctivitis and blepharitis; tuberculous, fungal or viral lesions of the skin or eye, including herpes simplex, dendritic keratitis, vaccinia or varicella; and conditions involving the posterior segment of the eye. They are also contraindicated in those individuals who have shown hypersensitivity to any of their components.

PRECAUTIONS: Extended ophthalmic use of topical steroid therapy may result in glaucoma with possible damage of the optic nerves, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids. As with any antibiotic preparation, prolonged use may result in the overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

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Research Triangle Park
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This instrument
was unheard of
just a few years ago.
Today this Shephard forceps is a basic
instrument in the dynamic area of intraocular
lens implantation.
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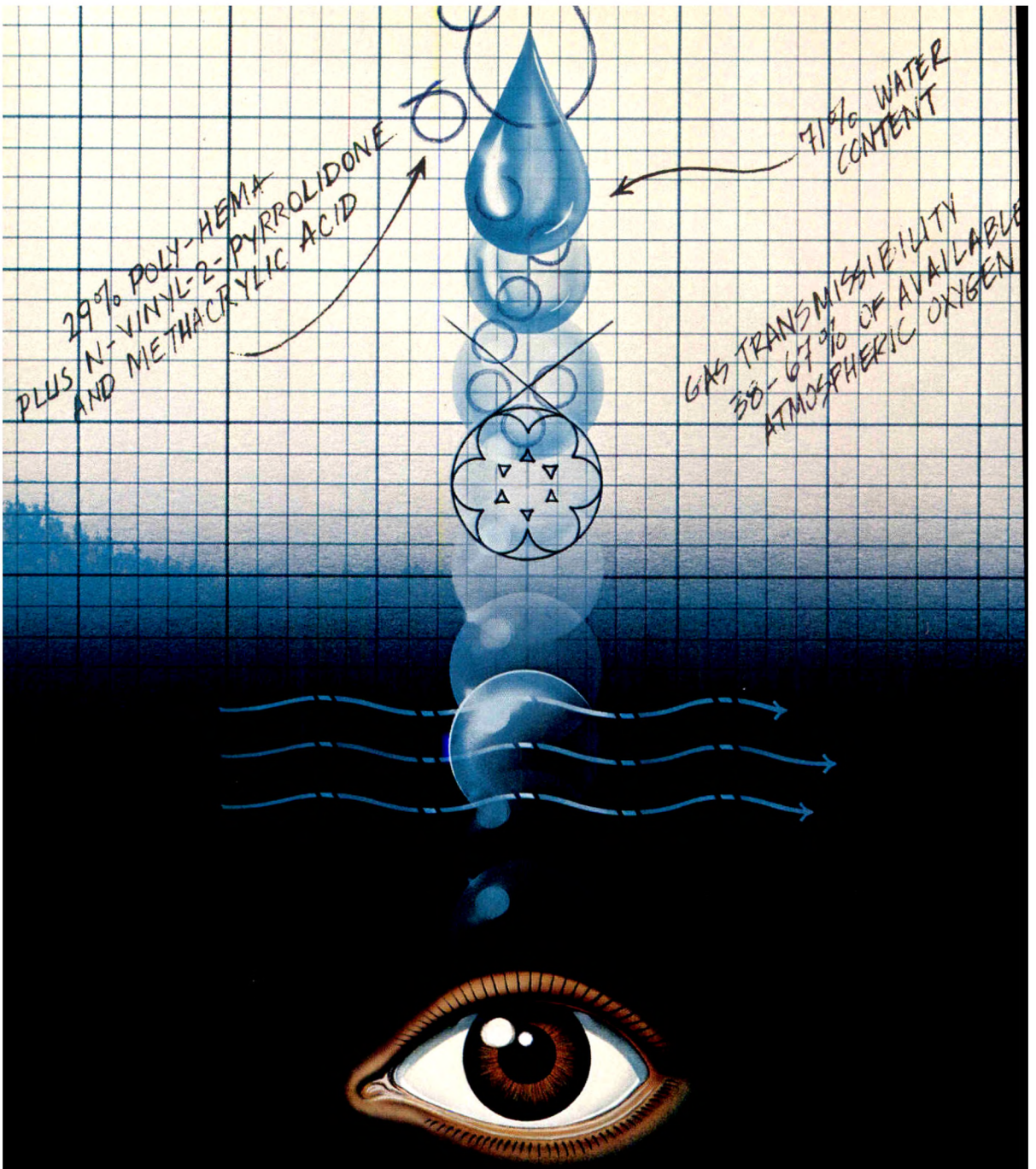

PERMALENS®

(PERFILCON A)

THE EXTENDED WEAR LENS

Permalens® Contact Lenses: not just extended wear of a lens, but a lens **designed specifically for extended wear.**

That's why Permalens® Contact Lenses are rapidly changing the field of vision correction. Now your aphakic patients can again experience near-normal vision from the moment they wake up in the morning. Without the bother of daily insertion and removal.

And because of their advanced design, Permalens® Contact Lenses exhibit a physiological response comparable to daily-wear soft lenses. Even though your patients wear them 24 hours a day, for weeks at a time. The long-term acceptance of Permalens® Contact Lenses has been proven through extensive clinical trials.

This response is partly due to the Permalens® material, perfilcon A, which combines high water content, high oxygen permeability, and dimensional stability. These properties were designed into the lens to facilitate oxygen transfer directly through the lens, so the cornea can receive an oxygen supply adequate to maintain itself in a healthy state.

These properties also make Permalens® Contact Lenses more supple, and therefore comfortable on the patient's eyes. Patients have reported, in fact, they're the next best thing to wearing no lens at all.

Easy to fit, Permalens® Contact Lenses are available in a range of powers from +11.00 to +17.00 diopters. And with just four parameters, the lens fits most corneal sizes and curvatures.

Maintenance, too, is uncomplicated. Since Permalens® Contact Lenses usually need only be removed once a month, cleaning and disinfection are simplified. The preferred regimen is Preflex®/Flexsol®/Normol.® (Thermal regimens can also be used.) For re-hydration during lens wear, Clērz® or Adapettes® eye drops are available.

Patient comfort and convenience . . . clinically proven safety . . . easy fitting . . . simple maintenance. Good reasons why thousands of patients and practitioners alike have accepted Permalens® as the extended-wear lens.

Permalens®
(perfilcon A)

Hydrophilic Contact Lens
For Extended Wear
Post-Cataract (Aphakic) Use

For full prescribing information, see next page.

Now available nation-wide. For details, contact your representative or call:

Cooper

Cooper Laboratories, Inc.
Permalens Division
265 N. Whisman Road
Mountain View, California 94043
(800) 227-8170
In California: (415) 968-1630
or (800) 982-5832

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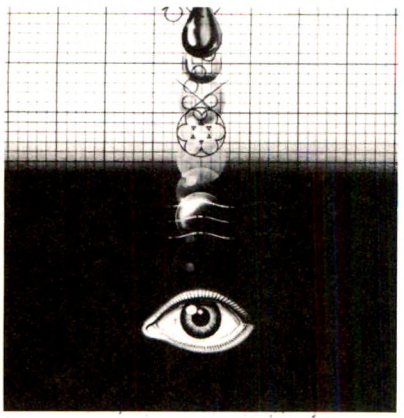

Permalens®
(perfilcon A)

Hydrophilic Contact Lens For Extended Wear Post-Cataract (Aphakic) Use

DESCRIPTION

The **Permalens®** (perfilcon A) Hydrophilic Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, perfilcon A, is a terpolymer of 2-hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone, and methacrylic acid, with ethyleneglycol dimethacrylate as a crosslinking agent. The hydrated lens consists of 29% perfilcon A and 71% water by weight. The gas permeability of **Permalens®** Hydrophilic Contact Lenses, using the Fatt method[1] has been determined to be: 42.0 x 10^{-11} cm^2•ml O_2/sec•ml•mm Hg at 36°C.

ACTIONS

When placed on the human cornea, the hydrated **Permalens®** Hydrophilic Contact Lens acts as a refracting medium to compensate spherical ametropias.

INDICATIONS AND USAGE

Aphakia

Permalens® (perfilcon A) Hydrophilic Contact Lenses are indicated for extended-wear aphakic vision correction in persons with non-diseased eyes.

Note: Supplemental spectacles may be required, in some conditions, to provide near vision or to compensate for uncorrected refractive astigmatism.

CONTRAINDICATIONS

Permalens® Hydrophilic Contact Lenses are contraindicated by the presence of any of the following conditions:

1. Acute and subacute inflammations of the anterior segment of the eye.
2. Any eye disease which affects the cornea or conjunctiva.
3. Insufficiency of lacrimal secretion.
4. Corneal hypoesthesia.
5. Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Abrasions and Infections

If a lens becomes less comfortable than it was when it was first placed on the wearer's cornea, the lens should be removed and inspected for the presence of a foreign body, lens coating, deposits, or lens damage. If examination of the patient's eye reveals any eye abrasion, ulceration, irritation or infection, or any other abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Patients should not be fitted with Permalens® (perfilcon A) Hydrophilic Contact Lenses during the post-operative period until, in the opinion of the surgeon, the eye has healed completely.

Medications and Eye Drops

Permalens® Hydrophilic Contact Lenses must be stored in an appropriate solution when off the eyes. The solution used is dependent on the system selected for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored in PERMASOL™ Rinsing and Storage Solution (sterile buffered balanced salt solution preserved with edetate disodium 0.1% and thimerosal 0.001%) or BOILnSOAK® Sterile Saline Solution (sterile buffered isotonic solution containing boric acid, sodium borate, sodium chloride 0.7%, preserved with Thimerosal (Lilly) 0.001% and edetate disodium 0.1%). When lenses are disinfected with the chemical disinfection system, they may be stored in FLEXSOL® Sterile Disinfection and Storage Solution (sterile buffered isotonic solution of sodium chloride, sodium borate, boric acid, polyvinylpyrrolidone, polyoxyethylene and polyoxypropylene, preserved with Thimerosal (Lilly) 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

Only the above solutions and the following may be used with **Permalens®** Hydrophilic Contact Lenses:

1. PREFLEX® Sterile Cleaning Solution (sterile solution of a nonionic cleaner preserved with Thimerosal (Lilly) 0.004% and edetate disodium 0.2%).
2. NORMOL® Sterile Rinsing Solution (sterile buffered isotonic aqueous solution of sodium chloride, sodium borate and boric acid, preserved with Thimerosal (Lilly) 0.001%, edetate disodium 0.1% and chlorhexidine 0.005%).
3. CLERZ® Lubricating and Rewetting Eye Drops (sterile solution preserved with edetate disodium 0.1% and Thimerosal (Lilly) 0.001%).
4. ADAPETTES® Sterile Lubricating Solution (buffered isotonic aqueous solution containing Adsorbobase® (polyvinylpyrrolidone with other water-soluble polymers), Thimerosal (Lilly) 0.004%, and edetate disodium 0.1%).

No conventional (hard) contact lens solution should be used. Only those solutions specifically recommended by your eye-care practitioner should be used during wear.

WEARING RESTRICTIONS

Permalens® (perfilcon A) Hydrophilic Contact Lenses should not be worn while swimming or in the presence of noxious or irritating vapors.

Lens-Care Regimen

Patients must adhere to the recommended lens-care regimen of **Permalens®** Hydrophilic Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections which might result in corneal ulcers.

PRECAUTIONS

Storage

Permalens® Hydrophilic Contact Lenses must be stored in the appropriate storage solution: PERMASOL™ Rinsing and Storage Solution, BOILnSOAK® Sterile Saline Solution, or FLEXSOL® Sterile Disinfection and Storage Solution, depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in one of the following until it returns to a hydrated (soft) pliable state:

1. PERMASOL™ Rinsing and Storage Solution
2. BOILnSOAK® Sterile Saline Solution
3. FLEXSOL® Sterile Disinfection and Storage Solution

PERMA-case™ Contact Lens Storage and Carrying Case should be used for storing lenses.

Hygiene

Hands must be washed and rinsed thoroughly, and dried before handling the lenses. Cosmetics, lotions, soaps and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Cleaning and Disinfecting

Prior to wearing, **Permalens®** (perfilcon A) Hydrophilic Contact Lenses must be both cleaned and disinfected.

Cleaning: Monthly removal for cleaning is recommended. However, at the discretion of the eye-care practitioner, the lenses may be removed at a frequency adjusted to the needs of each patient. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Sterile Cleaning Solution. Between regular cleaning periods, CLERZ® Lubricating and Rewetting Eye Drops or ADAPETTES® Sterile Lubricating Solution may be used to maintain lens hydration while being worn.

Routine Thermal Disinfection Method: Permalens® Hydrophilic Contact Lenses may be effectively disinfected using a low-heat disinfecting unit approved for use with hydrophilic contact lenses. After cleaning with PREFLEX® Sterile Cleaning Solution, rinse lenses with PERMASOL™ Rinsing and Storage Solution or BOILnSOAK® Sterile Saline Solution, and disinfect in a RINCON® low-heat Thermal Disinfection Unit or other approved unit. The lens storage containers must be emptied and filled with fresh PERMASOL™ Rinsing and Storage Solution or BOILnSOAK® Sterile Saline Solution just prior to disinfecting the lenses.

Alternate Thermal Disinfection Method: If a thermal unit is not available, the following disinfecting system can be used temporarily. After cleaning the lenses according to instructions, fill each chamber of the PERMA-case™ with PERMASOL™ or BOILnSOAK® Bring a pan of water to a rolling boil. Remove the pan from heat. Place the sealed carrying case into hot water and allow to cool. When the water is cool, lenses have been disinfected.

NOTE: USE OF THE RINCON® THERMAL DISINFECTION UNIT SHOULD BE RESUMED AS SOON AS POSSIBLE.

Chemical Disinfection Method: Disinfection with PREFLEX® Sterile Cleaning Solution, FLEXSOL® Sterile Disinfection and Storage Solution and NORMOL® Sterile Rinsing Solution has been shown to be an effective disinfection system. Following each removal, **Permalens®** Hydrophilic Contact Lenses must be cleaned with PREFLEX® Sterile Cleaning Solution and rinsed with NORMOL® Sterile Rinsing Solution. Each time the lens is stored, the PERMA-case™ Contact Lens Storage and Carrying Case must be emptied and refilled with fresh FLEXSOL® Sterile Disinfection and Storage Solution. Fresh FLEXSOL® Sterile Disinfection and Storage Solution must also be used when disinfecting a lens.

WARNING: FLEXSOL® STERILE DISINFECTION AND STORAGE SOLUTION SHOULD *NEVER* BE USED WI

LENS EJECTION

Occasionally, a lens may become partially dehydrated du sleep. This may result in the lens being dislodged from th lid action or rubbing the eyelids. Dislodged or routinely r lenses should be thoroughly rehydrated in one of the foll solutions:

1. PERMASOL™ Rinsing and Storage Solution
2. NORMOL® Sterile Rinsing Solution
3. BOILnSOAK® Sterile Saline Solution

After the lens returns to a soft, supple state it should be c and disinfected prior to replacement on the eye.

ADVERSE REACTIONS

Serious corneal damage may result from wearing lenses have been soaked in conventional hard contact lens solut Eye irritation may occur within a short time after putting o stored in a solution of improper pH or tonicity. Removal o lens will relieve the irritation.

Excessive tearing or redness, unusual eye secretions, red visual acuity, and photophobia are not normal; if these syn occur, the patient should be examined by an eye-care pra to determine the cause.

DOSAGE AND ADMINISTRATION

Fitting

Conventional methods of fitting contact lenses do not appl **Permalens®** (perfilcon A) Hydrophilic Contact Lenses. For detailed description of the fitting technique, refer to the **Pe lens®** Hydrophilic Contact Lens Professional Fitting Guide copies of which are available from Cooper Laboratories, In N. Whisman Road, Mountain View, California 94043.

WEARING SCHEDULE

Permalens® Hydrophilic Contact Lenses are indicated for extended-wear (24-hour) use, without a gradual daily increa wearing time required. Cleaning is recommended at month intervals. However, at the discretion of the eye-care practit the lenses may be removed at a frequency adjusted to the of each patient.

Lens Care and Handling

Care must be taken on the initial visit to ensure that the pati is supplied with all necessary accessory products and fully stands all care and handling instructions for the lenses. Reg post-fitting visits are necessary to assure patient health and compliance with instructions.

HOW SUPPLIED

Each lens is supplied sterile in a sealed glass vial containing a buffered isotonic salt solution. The vial is marked with the dioptric power, base curve, diameter, lot number, and expira date of the lens.

Accessories

Patient Care Kit	Cat. #8
Wearer's Manual	Cat. #8
PERMA-case™ Contact Lens Storage and Carrying Case	Cat. #8
FLEXSOL® Sterile Disinfection and Storage Solution*	Cat. #9
NORMOL® Sterile Rinsing Solution*	Cat. #9
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PERMASOL™ Rinsing and Storage Solution	Cat. #8
RINCON® Thermal Disinfection Unit**	Cat. #9
BOILnSOAK® Sterile Saline Solution*	Cat. #9
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CAUTION: Federal Law Prohibits Dispensing Without Prescription

[1]Fatt I. Morris JA: A survey of gas-permeable contact lenses *The Optician*: 27-36 (November 4, 1977).

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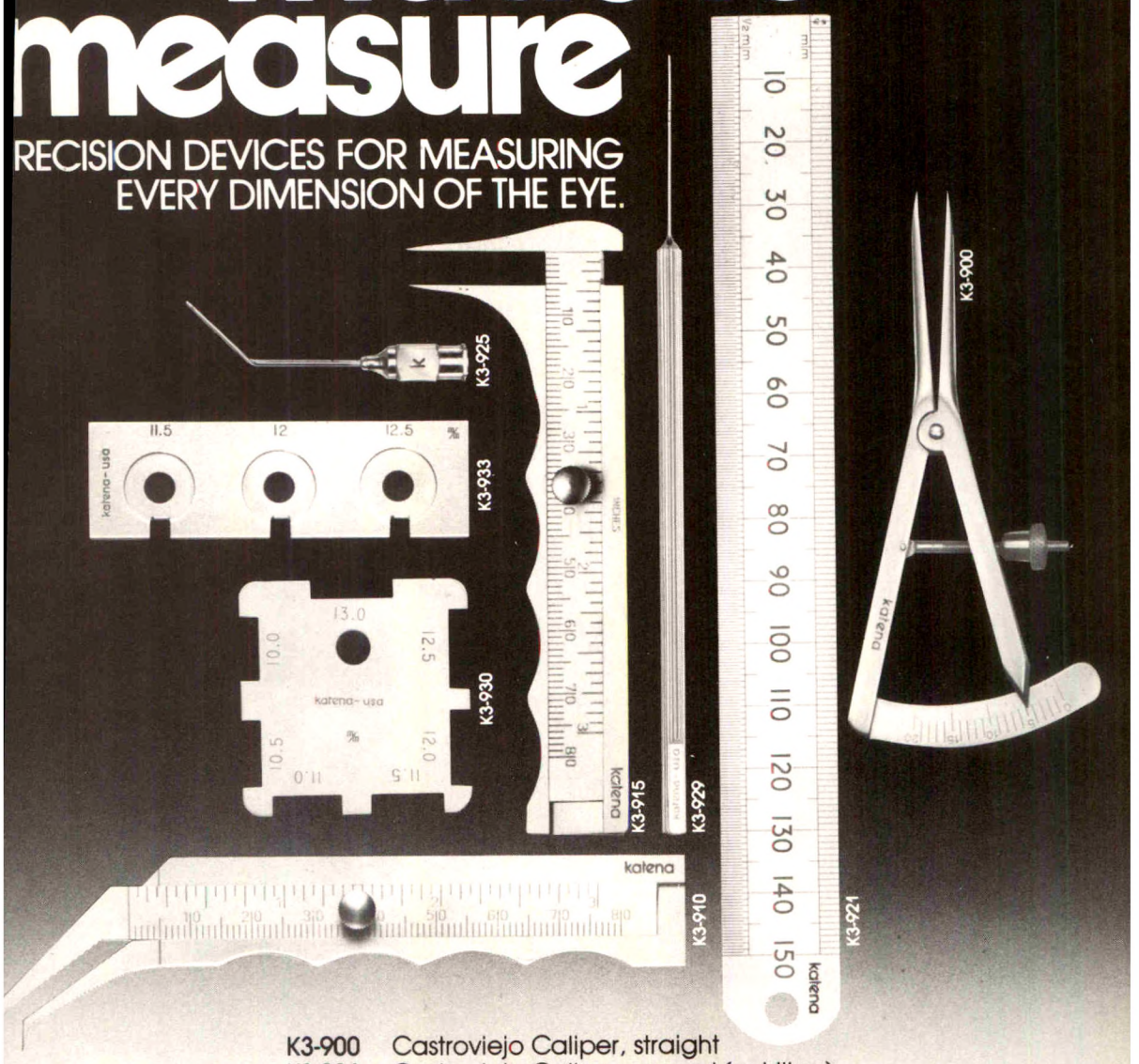

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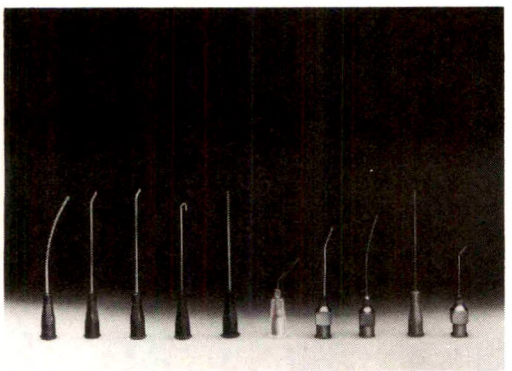
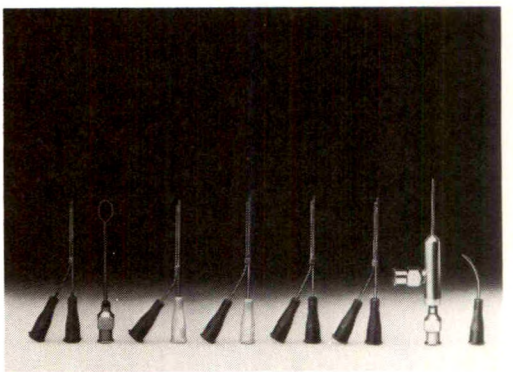


Left to right: Irrigating/Aspirating Cannula family—Curved, Posterior Capsule Polisher, Iris Retractor, U-shaped, Straight; Irrigating Cystotome, Anterior Chamber 16g, Lachrymal Cannula 26g, Retrobulbar 25g, Anterior Chamber 30g.



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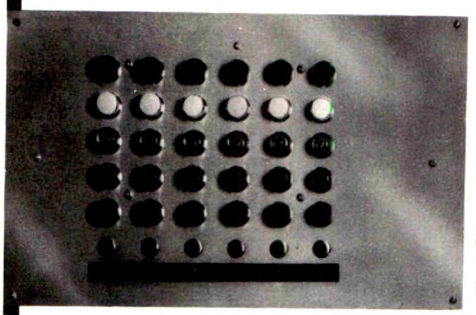

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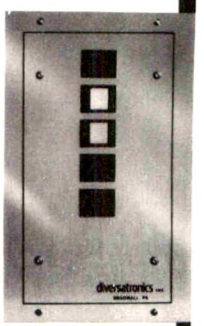

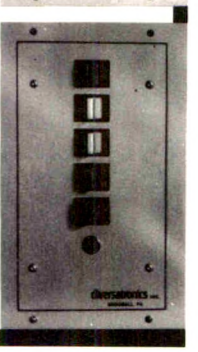

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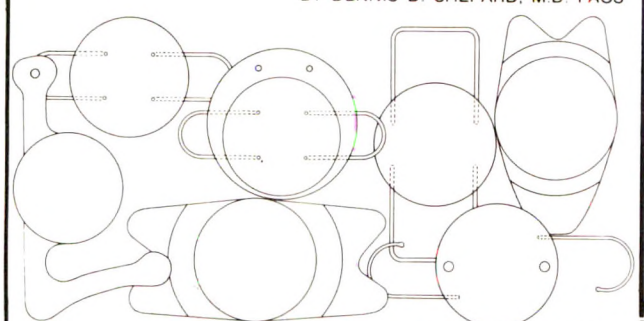

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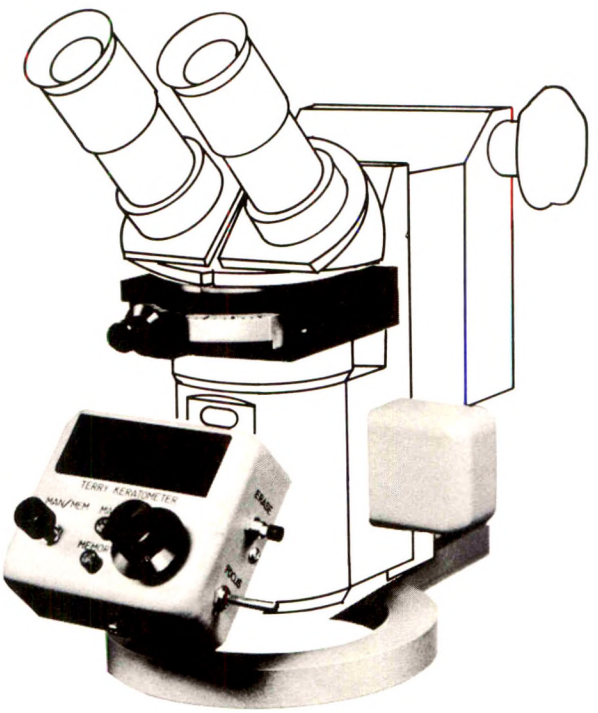

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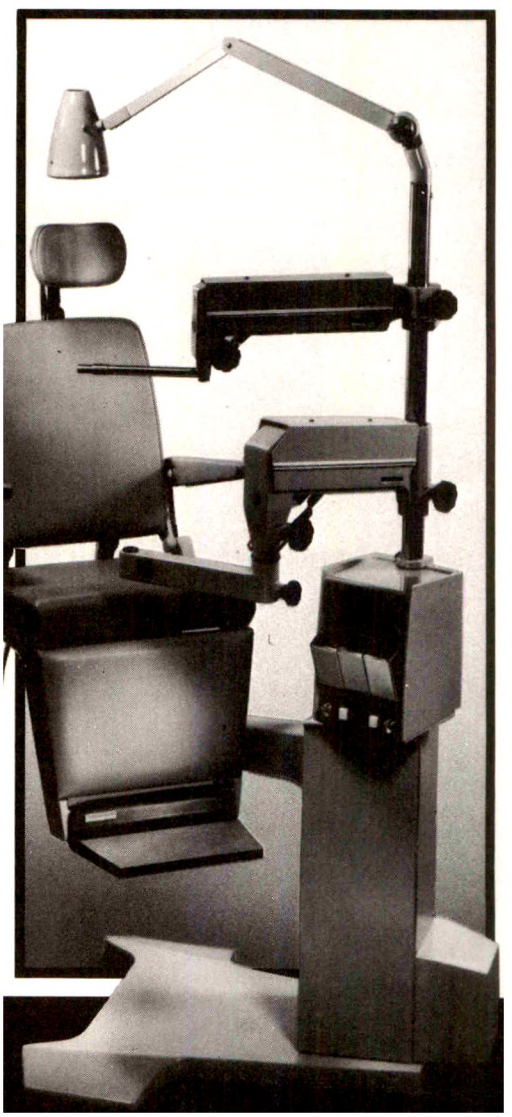

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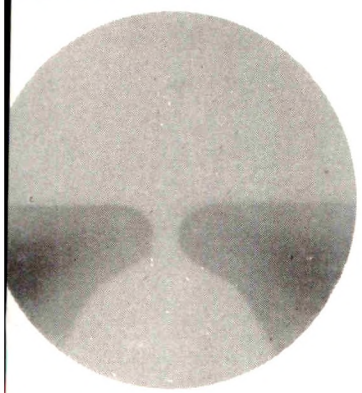

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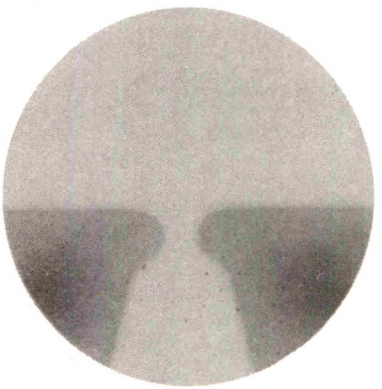

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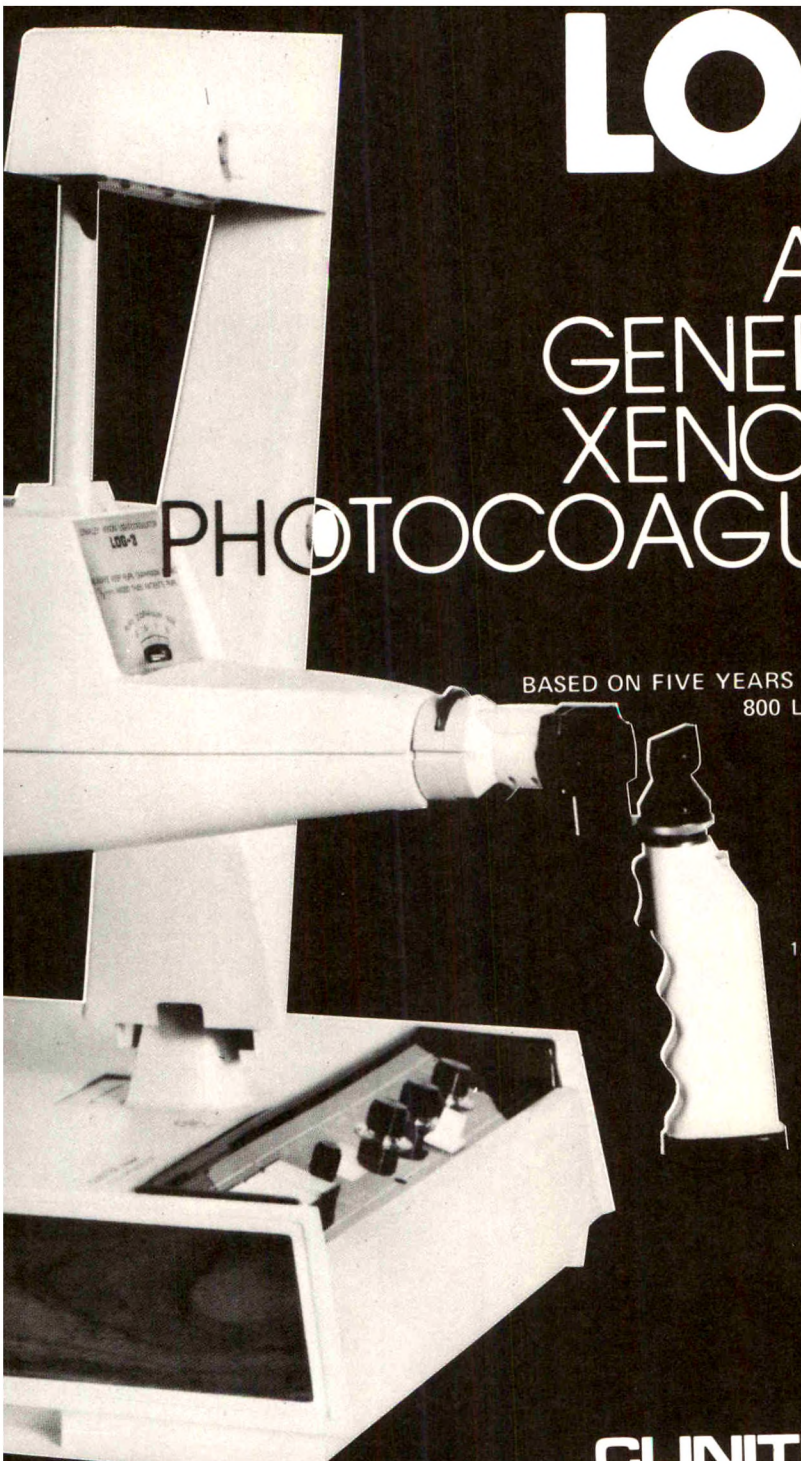
LOG 3

A THIRD GENERATION XENON ARC PHOTOCOAGULATOR



BASED ON FIVE YEARS OF EXPERIENCE AND OVER 800 LOG-2 PHOTOCOAGULATORS DELIVERED THROUGHOUT THE WORLD:

FEATURES:

- Thirty percent more power. ■
- 1.5° aperture for close macula work. ■
- Unique "optimatic" control; single dial setting for optimum chorio-retinal reaction. ■
- New contemporary design to complement today's hospital or office decor. ■
- Standard line voltage operation. ■
- Direct or indirect* ophthalmoscope delivery system. ■

Optional

CLINITEX division of
cooper medical devices corp.

☐ PLEASE SEND MORE INFORMATION
• ☐ PLEASE HAVE YOUR REPRESENTATIVE CONTACT ME

name _____ title _____

hospital or clinic _____

address _____

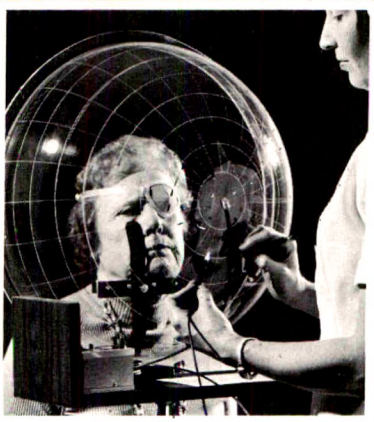
city _____ state _____ zip _____ phone _____

CLINITEX division of 183 newbury street / danvers, massachusetts 01923 / USA

UNIVERSAL PERIMETER

MOST EXACT CENTRAL	and/or	PERIPHERAL FIELDS
EXACT RAPID CONFRONTATION	and/or	PRECISE RECORDING
KINETIC	and/or	STATIC
FOR EVERY PRACTITIONER	and/or	PARAMEDICS
FOR SOLO PRACTICE	and/or	GROUPS or CLINICS
WHITE	or	RED

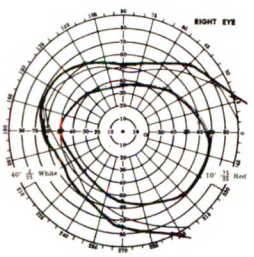
Fiber optics illuminates the fixation light and target with 60m Lamberts. Target sizes of 10′, 20′, and 40′ are adequate for almost all examinations.



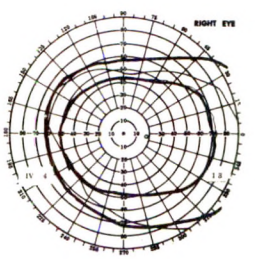
Clear Hemisphere

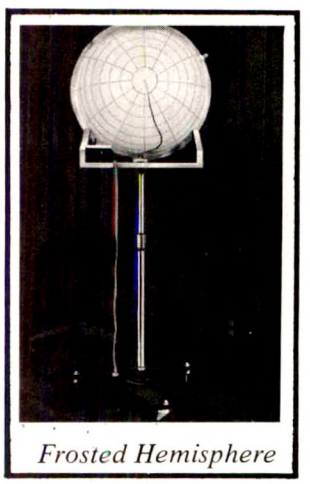
Central fields made with the Universal Perimeter compare favorably with those of the tangent screen because 10′ = 3/1000, 20′ = 6/1000, and 40′ = 12/1000, and 60 apostilbs is the luminance of a dull white object illuminated with 7.5 ft. candles. The 10′ white, similar to Goldmann III 4 isopter, extends almost to the full field. The 10′ red shows an enlarged blind spot and an isopter similar to the Goldmann I-3 and may detect the earliest central scotomas. Many find that the central fields are easier to take and are more reproducible than with the tangent screen. Peripheral fields are also easily done with the white targets. The clear hemisphere affords constant observation; the frosted-a uniform background. Only 4 square feet of space required, and stand with casters can be adjusted in seconds.

Universal Perimeter
16 yr. old healthy girl



Goldman Perimeter
38 yr. old healthy woman





Frosted Hemisphere

#921 Universal Perimeter, complete with fiber optics, caps for reducing the target size, Red and Black grease pencils, pad of special charts, and stand with casters (specify clear or frosted hemisphere) $345.00

Above, but without stand, for table mounting $270.00

WRITE TO THE
GOOD-LITE COMPANY
7426 Madison St., Forest Park, Ill. 60130 Phone 312/366-3860, or contact your dealer

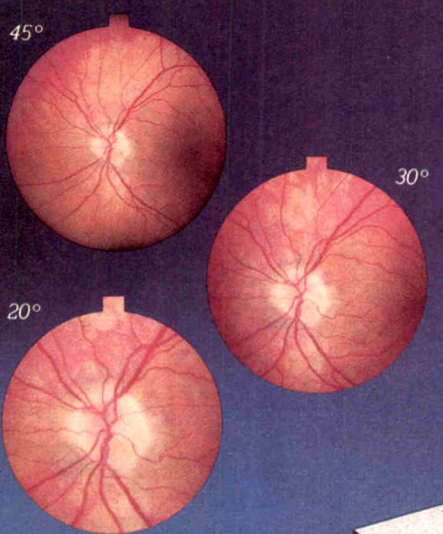
Variable Angle at the Flip of a Switch

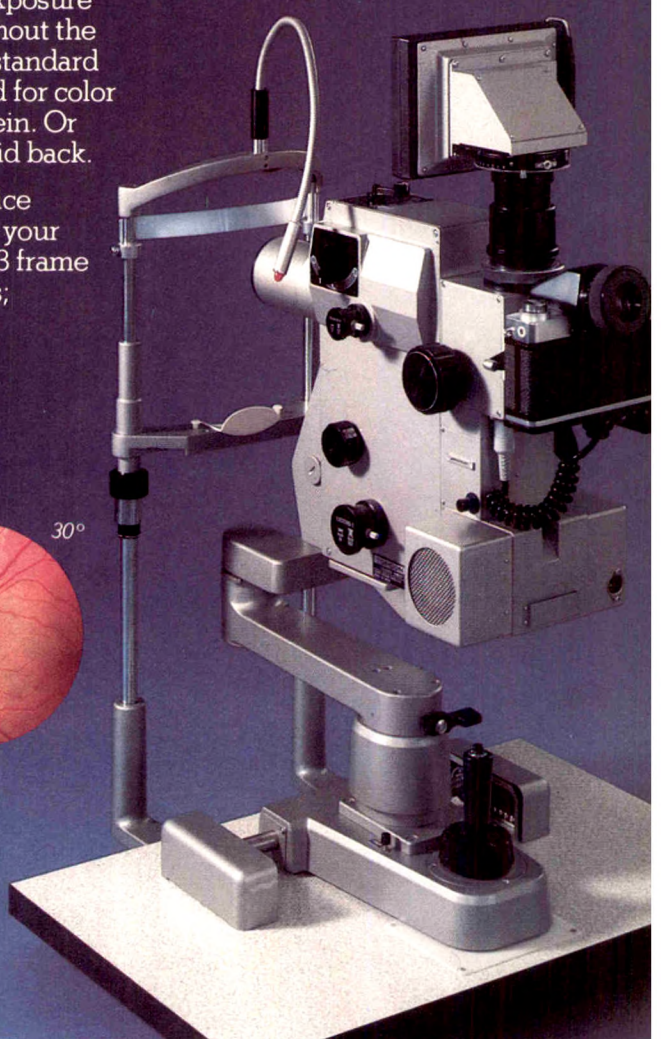
The Versatile Topcon TRC-W Retinal Camer

Once again Topcon moves forward the art of fundus photography. With a variable angle camera that lets you instantly switch between three different settings —45,° 30,° and 20° —for maximum operating flexibility.

The TRC-W produces superior fluorescein angiograms of the fundus *or* iris. At the specific magnifications that meet your needs, with correct exposure control maintained throughout the magnification range. Two standard camera bodies are supplied for color documentation or fluorescein. Or choose the optional Polaroid back.

You'll find the TRC-W's price equally accommodating to your needs. Available with 2 or 3 frame per second power supplies; standard or tilt models.





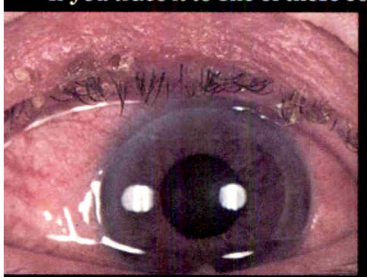
TOPCON

A New World of Precision Optics

Topcon Instrument Corp. of America, 9 Keystone Place, Paramus, New Jersey 07652

he infected eye–

If you trace it to one of these common problems...



*Acute bacterial conjunctivitis** Marked by itching or burning, hyperemia, lid edema and lacrimation or purulent discharge. Second only to refractive errors in frequency among ocular complaints.

*Bacterial corneal ulcer** Pain, photophobia, lacrimation and blepharospasm are usual presenting symptoms. Prompt institution of therapy is vital to avoid possible visual difficulty.

*When due to susceptible microorganisms.

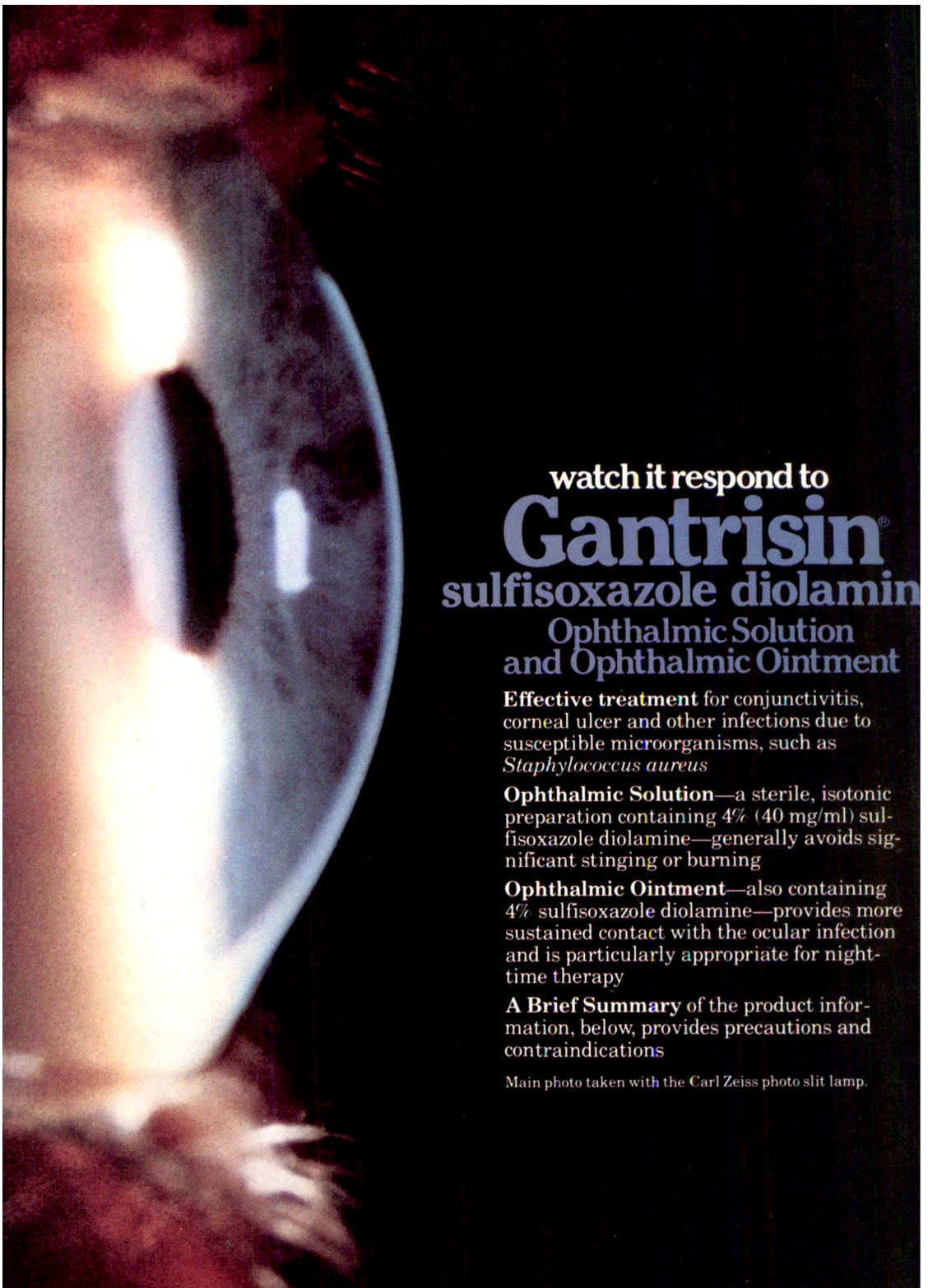
Gantrisin® **sulfisoxazole diolamine/Roche**
Ophthalmic Solution, Ophthalmic Ointment

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Conjunctivitis, corneal ulcer, other superficial ocular infections due to susceptible microorganisms; as adjunct in systemic sulfonamide therapy of trachoma.

Contraindications: Hypersensitivity.

Precautions: Incompatible with silver preparations; inactivated by para-aminobenzoic acid in purulent exudates; may increase growth of nonsusceptible organisms, including fungi. Ointment may retard corneal healing. Discontinue use if undesirable reactions occur.



watch it respond to

Gantrisin®

sulfisoxazole diolamin

Ophthalmic Solution and Ophthalmic Ointment

Effective treatment for conjunctivitis, corneal ulcer and other infections due to susceptible microorganisms, such as *Staphylococcus aureus*

Ophthalmic Solution—a sterile, isotonic preparation containing 4% (40 mg/ml) sulfisoxazole diolamine—generally avoids significant stinging or burning

Ophthalmic Ointment—also containing 4% sulfisoxazole diolamine—provides more sustained contact with the ocular infection and is particularly appropriate for nighttime therapy

A Brief Summary of the product information, below, provides precautions and contraindications

Main photo taken with the Carl Zeiss photo slit lamp.

Dosage and Administration: Solution: 2-3 drops in eye 3 or more times daily. Take care not to contaminate dropper. Ointment: small amount in lower conjunctival sac 1-3 times daily and at bedtime.

How Supplied:

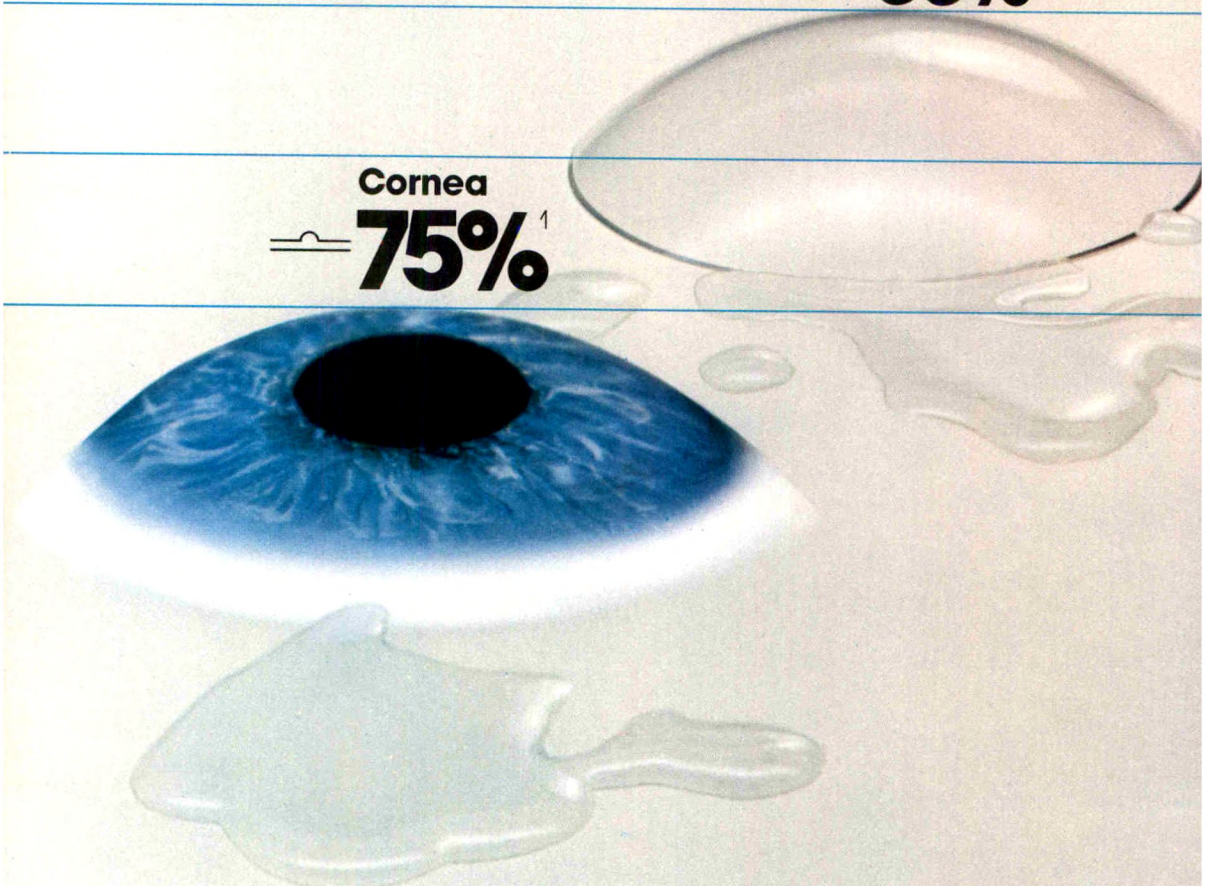
ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

THE BEST MATCH FOR YOUR PATIENT'S CORNEA

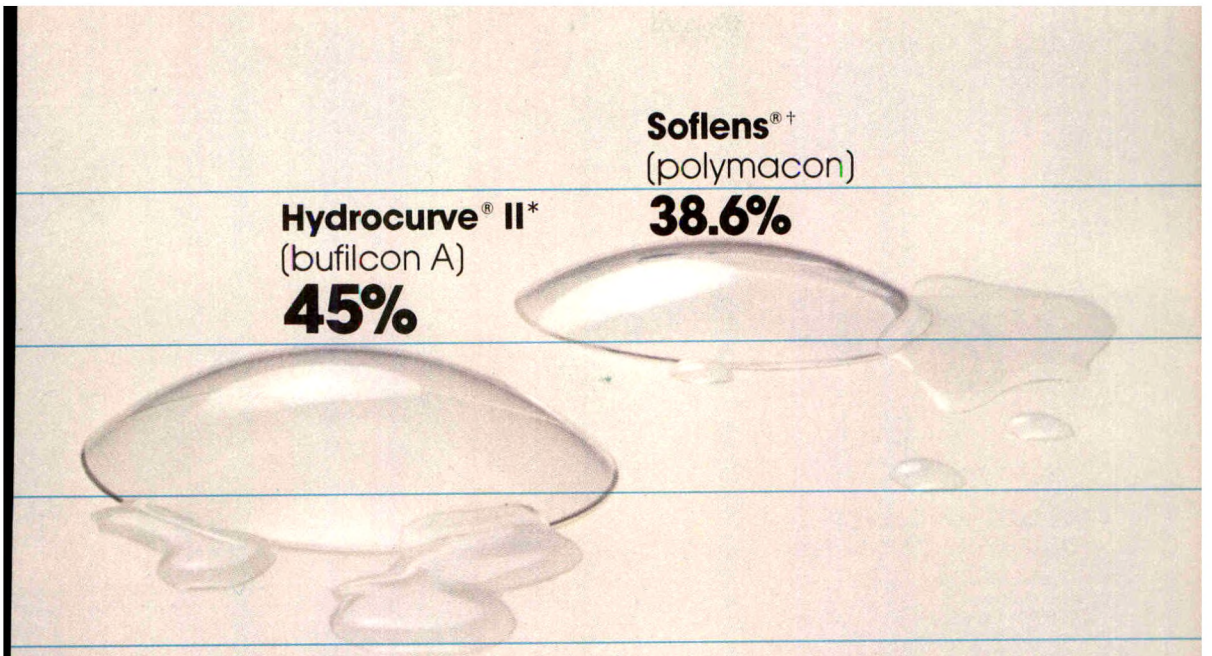
SOFTCON®
(vifilcon A)
55%

Cornea
75%[1]



© 1979 American Optical Corporation

*Hydrocurve is a registered trademark of Soft Lenses, Inc.
†Soflens is a registered trademark of Bausch & Lomb, In



Soft con® (vifilcon A) CONTACT LENS

OPTIMAL WATER CONTENT FOR A SOFT CONTACT LENS

Superior corneal compatibility SOFTCON lenses simulate the normal water environment of the cornea. Thus SOFTCON lenses encourage normal tear turnover, and are the only soft contact lenses for which no adaptation period is required.

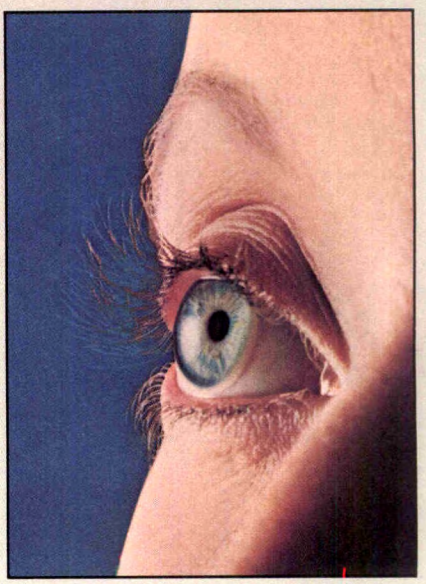
Enhanced permeability for better corneal nutrition The relatively high water content of SOFTCON lenses gives them enhanced permeability characteristics. In a comparative test of lenses with similar parameters, SOFTCON lenses were found to offer more than twice the water and oxygen permeability of Soflens® lenses.[2]

A good fit for your practice

- ☐ Available in a full range of powers: −8.00 to −0.25D, plano, +0.25 to +18.00D.
- ☐ Only six lens geometries needed to fit virtually all your patients —80% of patients can be fitted with three geometries alone.[3]
- ☐ Easy to adjust fit or power—fit and power are independent.

May we tell you more? For your copy of SOFTCON Highlights, the name of your SOFTCON Distributor, or any additional information—just call our toll-free number: 800 225-7750 (in Massachusetts, 617 765-9711).

American Optical Corp.
SOFT CONTACT LENS DIV.
Southbridge, MA 01550



Please see next page for full prescribing information.

Softcon®
(vifilcon A)
CONTACT LENS

THE BEST MATCH FOR YOUR PATIENT'S CORNEA

SOFTCON® (vifilcon A) Contact Lens
Vision Correction Use

DESCRIPTION The SOFTCON (vifilcon A) Contact Lens is a hemispherical flexible transparent shell which covers the cornea and part of the sclera. The lens is composed of vifilcon A, a soft hydrophilic plastic co-polymer of 2-hydroxyethyl methacrylate and povidone, USP. The chemical name is: Poly (2-hydroxyethyl methacrylate-co-ethylene dimethacrylate-co-methacrylic acid-g-povidone). When fully hydrated, the lens contains about 55% water by weight.

INDICATIONS The SOFTCON Contact Lens is indicated for the correction of visual acuity in persons with non-diseased eyes and in aphakia. It is indicated for persons who have spherical ametropias, refractive astigmatism usually 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS Presence of any active infection or inflammation of the eye, insufficient tears, corneal hypoesthesia or any systemic disease which may affect the eye adversely or be exaggerated by wearing contact lenses.

WARNINGS Medications and Eye Drops— The SOFTCON Contact Lens must be stored only in FLEXSOL® soaking solution. **NEVER USE CONVENTIONAL HARD CONTACT LENS PRODUCTS WITH THE SOFTCON CONTACT LENS.** No ophthalmic solutions or medications may be used by SOFTCON Contact Lens wearers immediately prior to or during wear of the lens. No solutions other than PREFLEX®, FLEXSOL, and NORMOL® used for cleaning and chemical disinfection may be used.

Aphakic Patients— Patients who have undergone surgery for cataract removal should not be fitted with SOFTCON Contact Lenses during the immediate post-operative period; until, in the opinion of the surgeon, the eye has healed completely.

Abrasions and infections— If a lens becomes less comfortable to the wearer than when it was first placed on the cornea, the lens should be removed immediately, and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a clinician must be consulted.

Lens Care—WEARERS MUST ADHERE TO THE RECOMMENDED DAILY CLEANING, CARE AND DISINFECTION REGIMEN AS DESCRIBED IN THE SOFTCON WEARER'S BOOKLET. FAILURE TO ADHERE TO THE RECOMMENDED PROCEDURES MAY RESULT IN THE DEVELOPMENT OF SERIOUS EYE INFECTION.

Wearing Restriction— The lens should be removed before sleeping or swimming, and should not be worn in the presence of irritating fumes or vapors.

Visual Blurring— If unusual visual blurring occurs, the lenses must be removed until the condition subsides. If blurring persists see your eye care practitioner.

PRECAUTIONS Storage— The SOFTCON Contact Lenses must be stored only in FLEXSOL soaking solution. If left exposed to air, the lenses will dehydrate, becoming hard and easily damaged. If a lens dehydrates, it should be carefully handled and soaked again in FLEXSOL until it returns to its normal soft, supple state.

Cleaning and Disinfection—THE SOFTCON (vifilcon A) CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER.

Cleaning— Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface from normal ocular secretions, airborne debris, or handling. The lenses must be cleaned before being disinfected, as deposits on the lens tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfection— Lenses must be disinfected daily according to the chemical disinfection regimen. For chemical disinfection, all three solutions, PREFLEX, FLEXSOL, and NORMOL, must be used and must be changed daily. In the event that the chemical disinfection materials are not available, the lenses should not be worn.

Hygiene— Hands must be washed, rinsed thoroughly and dried with a lint-free towel before handling the lenses. COSMETICS, lotions, soaps, oils and hand creams must not come in contact with the lenses since eye irritation may result. If aerosol sprays are used while the lenses are being worn, the eyes must be kept tightly closed until the sprays have settled.

Fluorescein— Use of fluorescein while the patient is wearing the lenses may cause the lenses to become discolored. Whenever fluorescein is used, irrigate the eyes with preserved normal saline solution, and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

ADVERSE REACTIONS Serious corneal damage may result from wearing lenses which have been soaked in conventional (hard) contact lens solutions.

Eye irritation may occur within a short time after applying a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely, a lens may adhere to an eye as a result of a patient sleeping with the lens on or while wearing a hypotonic lens. If a lens adheres for any reason, apply a few drops of ADAPETTES® directly to the eye and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around lights, or visual blurring may occur if lenses are worn for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. If symptoms do not subside promptly, or if excess tearing, unusual secretions, or photophobia develop, professional consultation should be obtained.

DOSAGE AND ADMINISTRATION Fitting— Usu methods of fitting conventional (hard) contc lenses do not apply to the SOFTCON Conta Lens.

For a detailed description of the fitting technique, refer to the SOFTCON Fitting Boo

Wearing Schedule— The wearing schedule be determined by the eye care practitioner Studies have not been performed to suppo the safety of this lens for longer than the recommended wearing time.

Patients should wear their lenses for 8-16 h on the day the lenses are dispensed. If patie cannot tolerate 16 hours of lens wear daily, th eyes should be examined and the lens fit re-evaluated.

Lens Care and Handling— Care must be ta the initial visit to assure that the patient is supplied with a SOFTCON Care Kit and fully understands all proper care and handling procedures for the lenses. As with any conta lens patient, regular re-examination visits are necessary to assure ocular health and patie compliance with instructions.

How Supplied— Each lens is shipped sterile i sealed glass vial containing buffered normc saline solution. The vial label is marked with th base curve, dioptric power, diameter and th manufacturing identification number of the l

Patient Care Kit— The SOFTCON (vifilcon A) C Kit is a package required for cleaning, disinfection and storage of the lenses. It cons of the following:

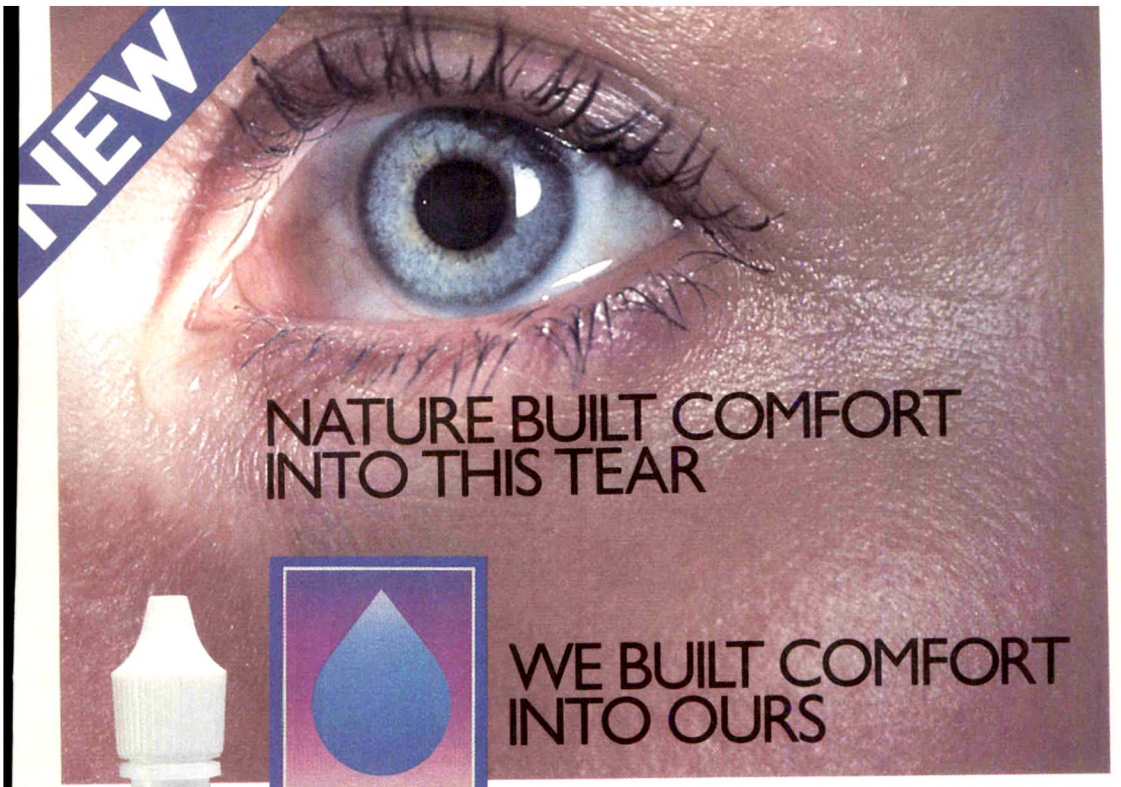
- Carrying & Storage Lens Case
- PREFLEX® Sterile Cleaning Solution
- FLEXSOL® Sterile Disinfection and Storage Solution
- NORMOL® Sterile Rinsing Solution
- ADAPETTES® Sterile Lubricating Solution
- SOFTCON Wearer's Booklet

Caution: Federal law prohibits dispensing without prescription.

PREFLEX®, FLEXSOL®, NORMOL®, and ADAPETTES®, Trademarks of Burton, Parsons & Co., Inc.

References: 1. Graymore CN: Biochemistry of the Ey Academic Press, London, p 7. 2. Morrison DR, Edelhauser HF: Permeability of hydrophilic contact lenses. Invest Ophthalmol 11(1):58-63, January 1972. 3. Data on file, Soft Contact Lens Div., American Optical Corp., Southbridge, MA 01550.

American Optical Corp.
SOFT CONTACT LENS DIV.
Southbridge, MA 01550



TEARS PLUS™

THE COMFORTABLE ARTIFICIAL TEAR.

In a clinical study conducted by a private practitioner on 93 patients, more than 4 out of 5 felt Tears Plus was comfortable in the eye[1]

COMFORT IS BUILT INTO THE NEW TEARS PLUS FORMULATION.

Burning, scratchy, gritty, dry eyes are soothed by the **polyvinyl alcohol. Povidone** increases the polymer protection concentration to provide enhanced lubrication —without increased viscosity. Combine these in a **nonbuffered, isotonic** solution that adjusts to the pH of the eye quickly and avoids stinging and you've got the comfort your patients want. And deserve.

RECOMMEND TEARS PLUS: IT'S THE TEAR WITH COMFORT BUILT IN.

AND REMEMBER LIQUIFILM® TEARS FOR YOUR PATIENTS WHO WANT AN ALTERNATIVE COMFORTABLE, ECONOMICAL ARTIFICIAL TEAR.

Reference: 1. Allergan Report Series No. 162, 1979.

ALLERGAN Pharmaceuticals, Inc.
Irvine, CA 92713

An effective agent available for the reduction of corneal edema

MURO 128

5% sodium chloride sterile ophthalmic ointment and solution

ADVANTAGES

- Single entity—sodium chloride
- Flexibility of dosage
  - Sterile ophthalmic ointment
  - Sterile ophthalmic solution
- 5% sodium chloride
- Time-tested

OINTMENT

- Prolonged retention on cornea
- Less burning and stinging

SOLUTION

- Addition of methylcellulose
- Added viscosity

MURO 128 OINTMENT AND SOLUTION

- Greater reduction of corneal edema
- Better patient compliance

MURO 128
(Sodium Chloride 5% Ointment)

DESCRIPTION: A sterile ophthalmic ointment of sodium chloride 5% in a base of lanolin, liquid petrolatum and white petrolatum.

MURO 128
(Sodium Chloride 5% Solution)

DESCRIPTION: A sterile ophthalmic solution of sodium chloride 5% with methylcellulose 0.9%. Also contains methylparaben 0.023% and propylparaben 0.01% as preservatives, and purified water.

INDICATIONS: As an aid for reducing edema in conditions of the cornea from various causes as bullous keratitis, keratopathy and following cataract surgery and Fuchs' endothelial-epithelial dystrophy.

CONTRAINDICATED: Hypersensitivity to any ingredient.

ADVERSE REACTION: Slight stinging sensation which is usually transient in nature.

OINTMENT DOSAGE: One or more times a day as directed by physician.

HOW SUPPLIED: As a sterile ophthalmic ointment in 3.5g tubes. Keep tightly closed—store in a cool place.

SOLUTION DOSAGE: 1 or 2 drops in affected eye(s) three times a day, or as directed by the physician.

HOW SUPPLIED: 15 ml and 30 ml plastic dropper bottles. Keep tightly closed—store in a cool place.

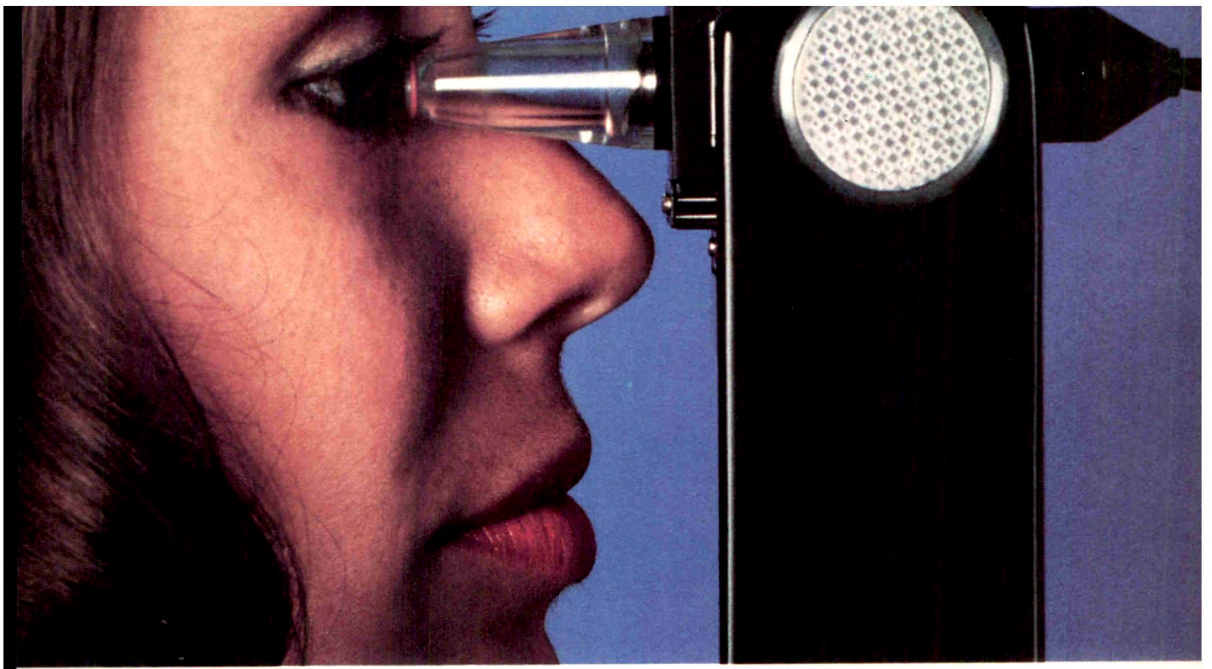
CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription.

WARNING: For topical ophthalmic use only. Do not touch tip of tube or dropper tip to any surface since this may contaminate ointment or solution.

* Luxenberg, M.N., and Greek, K.: Reduction of Corneal Edema with topical hypertonic agents. Am. J. Ophth. 71:847, 1971.

MURO OPHTHALMICS

MURO PHARMACAL LABORATORIES, INC.
890 East St., Tewksbury, Mass. 01876
Tel. (617) 479-2680, 851-2557



Measurements, not estimates of IOL power

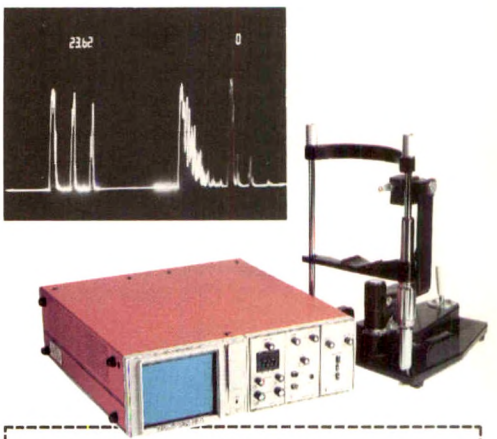
The DBR-300 brings extreme precision to intraocular lens power determinations. Accuracy to within a quarter of a diopter has been proven in clinical use for over 4 years. And maximum performance is maintained even in cases of dense, mature cataracts.

Axial length measurements are digitally displayed along with the A-scan trace, and the probe mounting design minimizes globe distortion and patient discomfort. The result: rapid, simple examinations conducted in minutes, easy documentation, and maximum performance. The Digital Biometric Ruler Model DBR-300 is as easy to operate as an applanation tonometer. Full A-mode diagnostic capabilities also permit detection and diagnosis of ocular and orbital pathology.

The instrument's modular construction allows rapid service and economical upgrading to add future developments. The clinically proven Ocuscan-400 real-time, A and B-mode, contact scanner can be added through modification of one module, at considerable savings.

Accurate. Reliable. Clincally proven. The DBR-300 gives you the data needed to minimize dioptric errors. Sonometrics also provides the most advanced system for IOL calculations: the Binkhorst module for easy use in the Texas Instruments TI-58/59 printing calculators.

And the DBR-300 is fully backed by the technical services and assistance of Sonometrics, the first and most advanced company in ophthalmic ultrasound. Call toll-free (800) 223-0412 or mail the coupon at right for additional details.



DBR-300/Sonometrics Systems, Inc.
16 West 61st Street, New York, New York 10023
AJO-2

Name_____

Affiliation_____

Address_____

City_____ State_____ Zip_____

Phone_____

DBR-300
DIGITAL BIOMETRIC RULER
SONOMETRICS SYSTEMS, INC

A Rorer Group Company

SUPRAMID EXTRA®

The Tissue-Friendly, Cable-type, Nylon-6 suture from S. Jackson, Inc.

—proven in all types of surgery for 30 years

- THE inert polyamide
- Non-absorbable
- Long-lasting in tissue
- Extremely strong
- Ties easily...with fewer knots
- Stays tied

SUPRAMID EXTRA® sutures in sterile packages

- Sizes 10-0 to 0 with swaged-on needles (sizes 1, 3, and 8 also available)
- Needles by *Sharpoint®*: Spatulated, Reverse Cutting, Taper Point. Also special needles with von Noorden, Knapp, and Yasargil design. Guibor design frontalis-Fixation "ski" needles. All needles attached to appropriate sizes of Supramid Extra suture.

The same inert **SUPRAMID®** material is now available as:

SURGICAL FOIL ..... smooth surface or "Guibor-design" orange-peel surface for orbital floor blow-out fracture repair and other oculo-plastic surgery.

EYE MUSCLE SLEEVES ..... for preventing eye muscle adhesions, as developed by Edward A. Dunlap, M.D.

QUARTER-GLOBE CAPS ..... for adhesion prevention according to Philip Knapp, M.D.

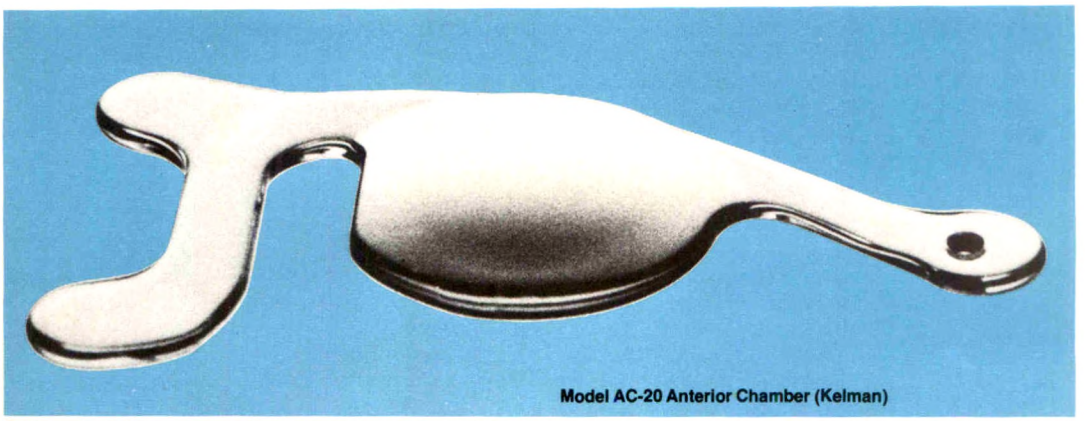
MESH ..... for rhinoplasty and mentoplasty augmentation

For information and catalog write or call
S. JACKSON, INC. (Dept. J)
4815 Rugby Ave.,
Washington, D.C. 20014

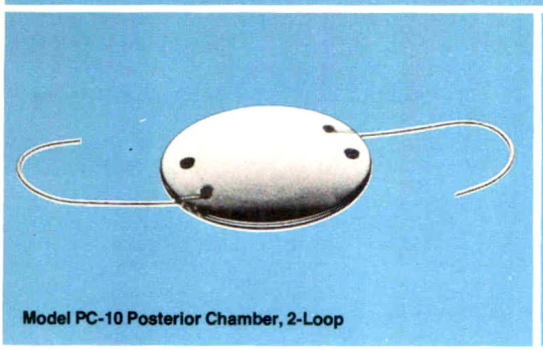
Phone: 301-657-8920

HEYER SCHULE
MEDICAL OPTICS CENTER

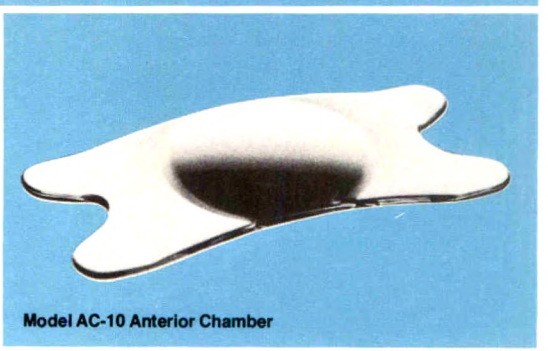
Innovations for Ophthalmology



Model AC-20 Anterior Chamber (Kelman)



Model PC-10 Posterior Chamber, 2-Loop



Model AC-10 Anterior Chamber

UNRETOUCHED PHOTOGRAPHS

Heyer-Schulte intraocular lenses[1] are precision designed and are lathe-cut and polished from Perspex CQ. Deliberate and precise fabrication methods, and the research capabilities of American Hospital Supply Corporation, have resulted in lenses of high quality and workmanship that are immediately recognized by the implanting surgeon.

Heyer-Schulte has developed a proprietary process that results in *all* edges being fully radiused and finely polished.

The Kelman Anterior Chamber Lens is used following intracapsular *and* extracapsular cataract extraction. The lens, which has three point fixation, can be inserted through a small 5mm. incision, making it a better choice for secondary implantation. Due to its unique design, the Kelman lens is very flexible and is lighter than other anterior chamber lenses. Tenderness-on-touch has been reported to be greatly reduced.

As in the AC-10 anterior chamber lens, the "vault" of the optic is a consistent 0.5mm. and lenses are available in haptic diameters from 11.5mm to 13.5mm in .5mm steps. Lenses from 15.0 D to 22.0 D are available in .5 D increments.

Heyer-Schulte is currently sponsoring instructional courses on implantation of Kelman anterior chamber lenses. Please ask us for complete details.

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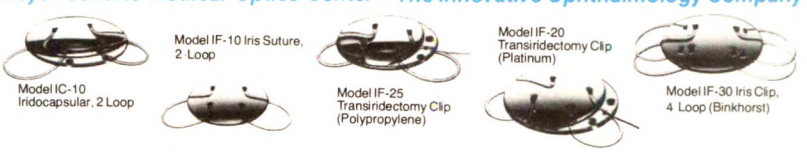

Model IC-10 Iridocapsular, 2 Loop
Model IF-10 Iris Suture, 2 Loop
Model IF-25 Transiridectomy Clip (Polypropylene)
Model IF-20 Transiridectomy Clip (Platinum)
Model IF-30 Iris Clip, 4 Loop (Binkhorst)

[1]Intraocular lenses are investigational devices, limited by U.S. law to investigational use.

[2]Sauflon lenses are investigational devices and are not commercially available.

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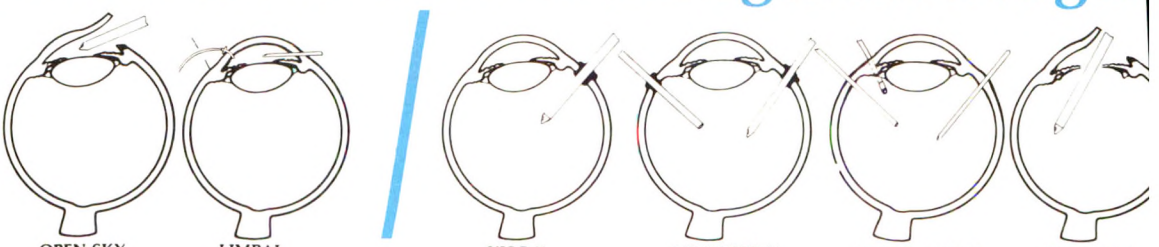

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- Oscillating, forward, reverse cutting modes - variable to 1,080 cuts per minute.
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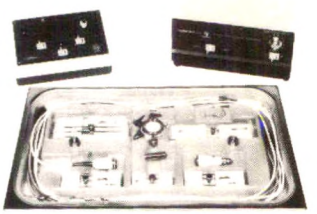
- Automatic suction/reflux achieves instantaneous pressure equilibrium within the eye. Manual suction if desired.

The VISC-X is lightweight and modular - assembles in seconds without tools. Rechargeable battery operation for patient safety. Surgery is aided greatly by use of special double lip, self-sharpening cutting tips which exert no traction on tissue or vitreous.

The VISC-X is a revolutionary new concept in systems for anter posterior segment surgery. It permits the surgeon to employ a wide variety of techniques through singular or multiple incisio Using the modular building block approach, the surgeon can create a system customized for present requirements and preferences. As needs change, the VISC-X systems may be expanded to permit additional techniques and procedures.



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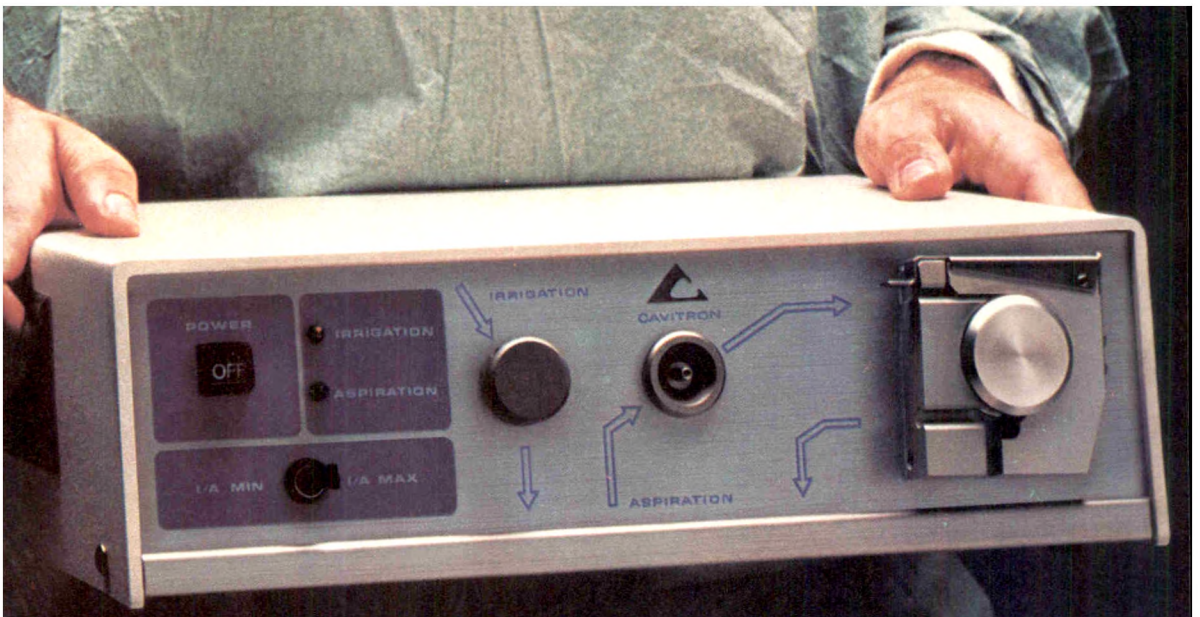

The new alternative for extracapsular procedures.

Cavitron E.I.S.™

The Cavitron Extraction - Irrigation System (E.I.S.), Model 6500, provides the surgeon with a reasonably priced instrument for precise control over irrigation and aspiration. While not a substitute for the widely used and clinically proven Cavitron/Kelman® Phaco-Emulsifier® aspirator, it makes an ideal replacement for push-pull syringe or squeeze bulb techniques. The Model 6500 allows an extracapsular procedure to be performed with an intact posterior capsule and a clean posterior chamber. Applications include planned extracapsular cataract extractions preceding intraocular lens implants and traumatic and congenital cataracts when lens fragmentation may not be required.

The key to the E.I.S. is the proven vacuum control system developed by Cavitron. During the procedure, a sterile irrigating fluid is introduced into the anterior chamber to replace aspirated fluid and materials. A relatively stable pressure is maintained within the anterior chamber which provides a safeguard against excessive, rapid changes in intraocular pressure. The surgeon can select one of two vacuum levels to meet varying requirements. Time spent in the anterior chamber is minimal.

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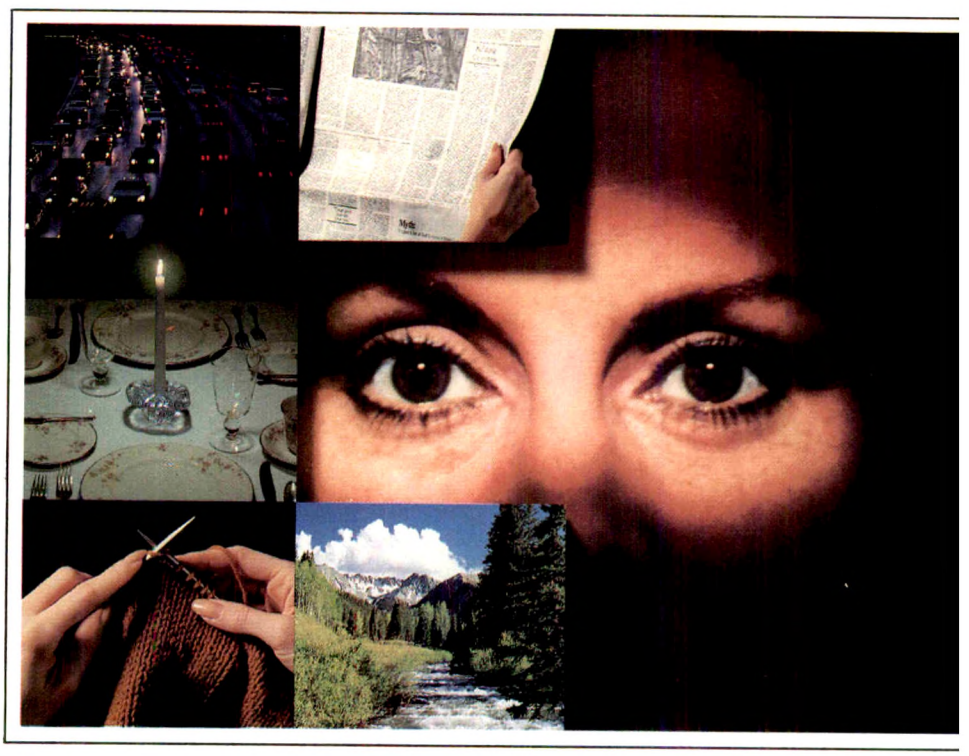
In chronic open-angle glaucoma therapy

Two good reasons to switch patients to



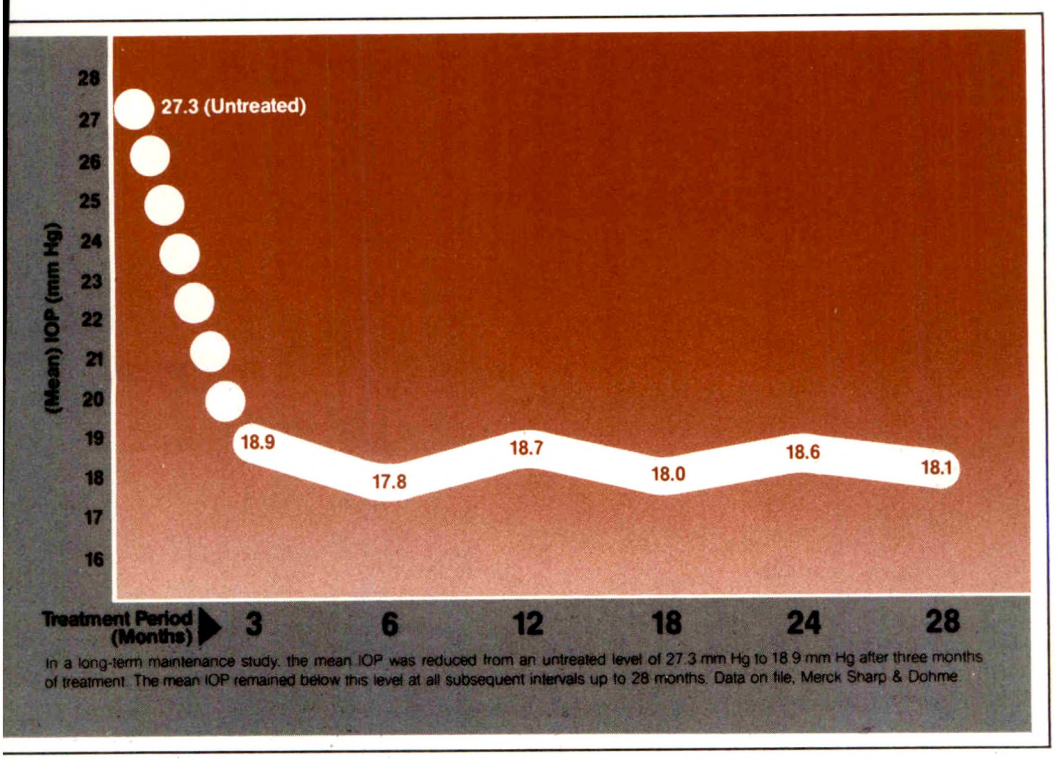
1. A better quality of life for many patients...

Patients on TIMOPTIC® (Timolol Maleate, MSD) generally do *not* experience the following therapy-limiting side effects:

change in pupil size/dimming of vision/night blindness*

TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product. Occasionally, mild ocular irritation has been reported.

Timoptic®
(TIMOLOL MALEATE | MSD)
OPHTHALMIC SOLUTION



In a long-term maintenance study, the mean IOP was reduced from an untreated level of 27.3 mm Hg to 18.9 mm Hg after three months of treatment. The mean IOP remained below this level at all subsequent intervals up to 28 months. Data on file, Merck Sharp & Dohme.

2. Efficacy maintained in long-term therapy...

- No tolerance was observed in 102 patients for 28 months
- TIMOPTIC was significantly more effective than pilocarpine or epinephrine in reducing elevated IOP*
- TIMOPTIC reduced IOP in 3 out of 4 patients*

*Based on controlled multiclinic studies, evaluating over 1000 patients.

MSD MERCK SHARP & DOHME

For a brief summary of Prescribing Information, please see following page. Copyright © 1979 by Merck & Co., Inc.

Timoptic®

(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution

a significant advance for the reduction of IOP in:

- chronic open-angle glaucoma
- aphakic glaucoma
- some patients with secondary glaucoma
- ocular hypertension
- some patients who respond inadequately to multiple antiglaucoma drug therapy

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in each eye twice a day.

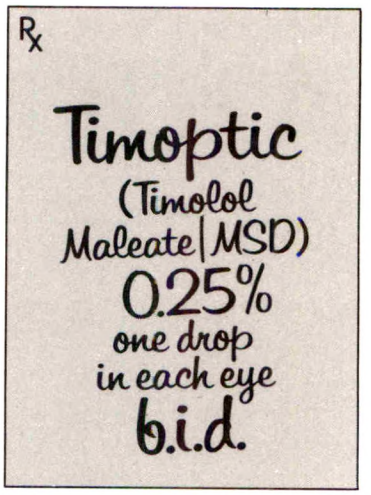
How to transfer from current therapy to TIMOPTIC:
1. On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC in each eye b.i.d.

2. On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC in each eye b.i.d.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in each eye. Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in each eye.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.



CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.

Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.

Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.

ADVERSE REACTIONS: Occasionally, signs and symptoms of mild ocular irritation have been reported. Local hypersensitivity reactions, including localized and generalized rash, have occurred rarely.

Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Rarely, episodes of acute bronchospasm have been reported in patients with bronchospastic disease (see PRECAUTIONS).

Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studied in patients wearing lenses made with materials other than PMMA.

HOW SUPPLIED:
TIMOPTIC Ophthalmic Solution, 0.25%
TIMOPTIC Ophthalmic Solution, 0.5%
Both are available in 5-ml and 10-ml plastic OCUMETER® Ophthalmic Dispensers with a controlled drop tip.
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For more detailed information, consult your MSD representative and the full Prescribing Information.
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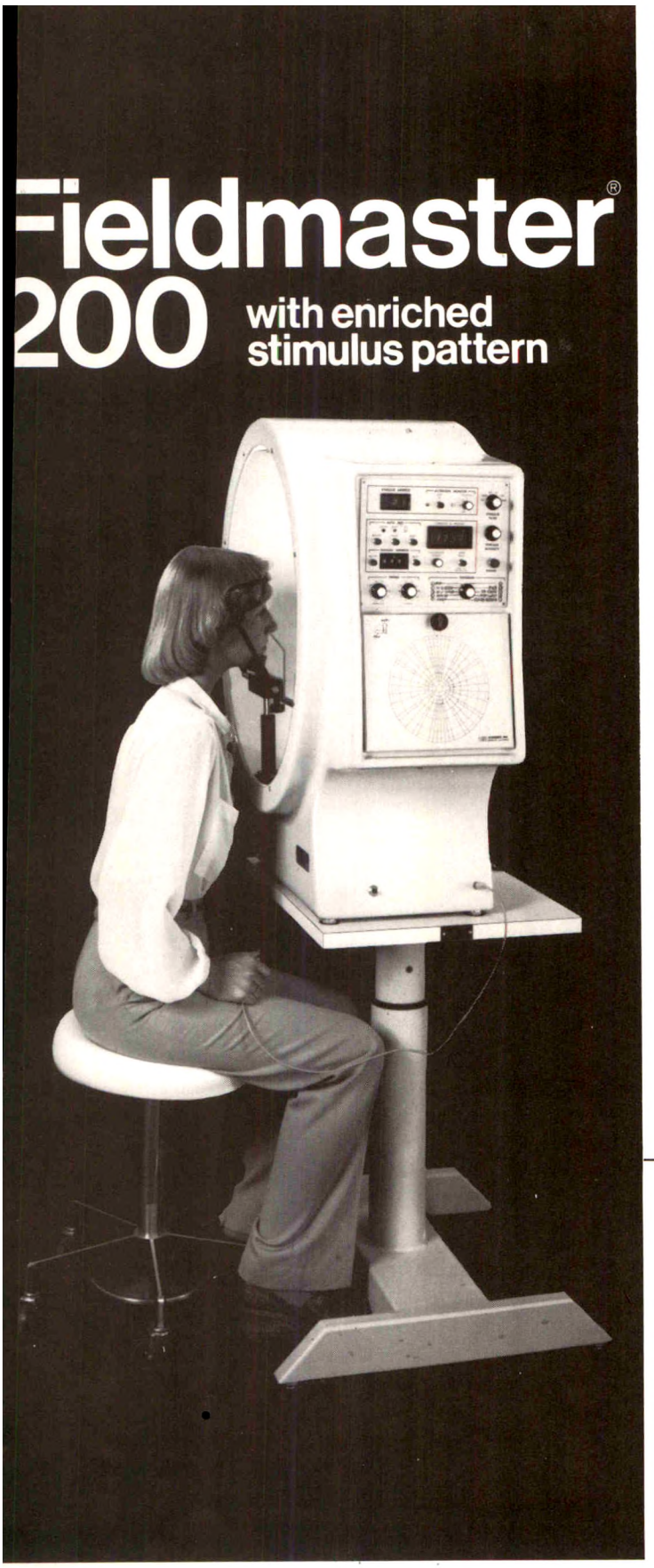
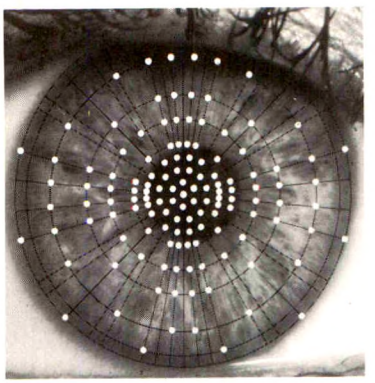
Fieldmaster® 200 with enriched stimulus pattern





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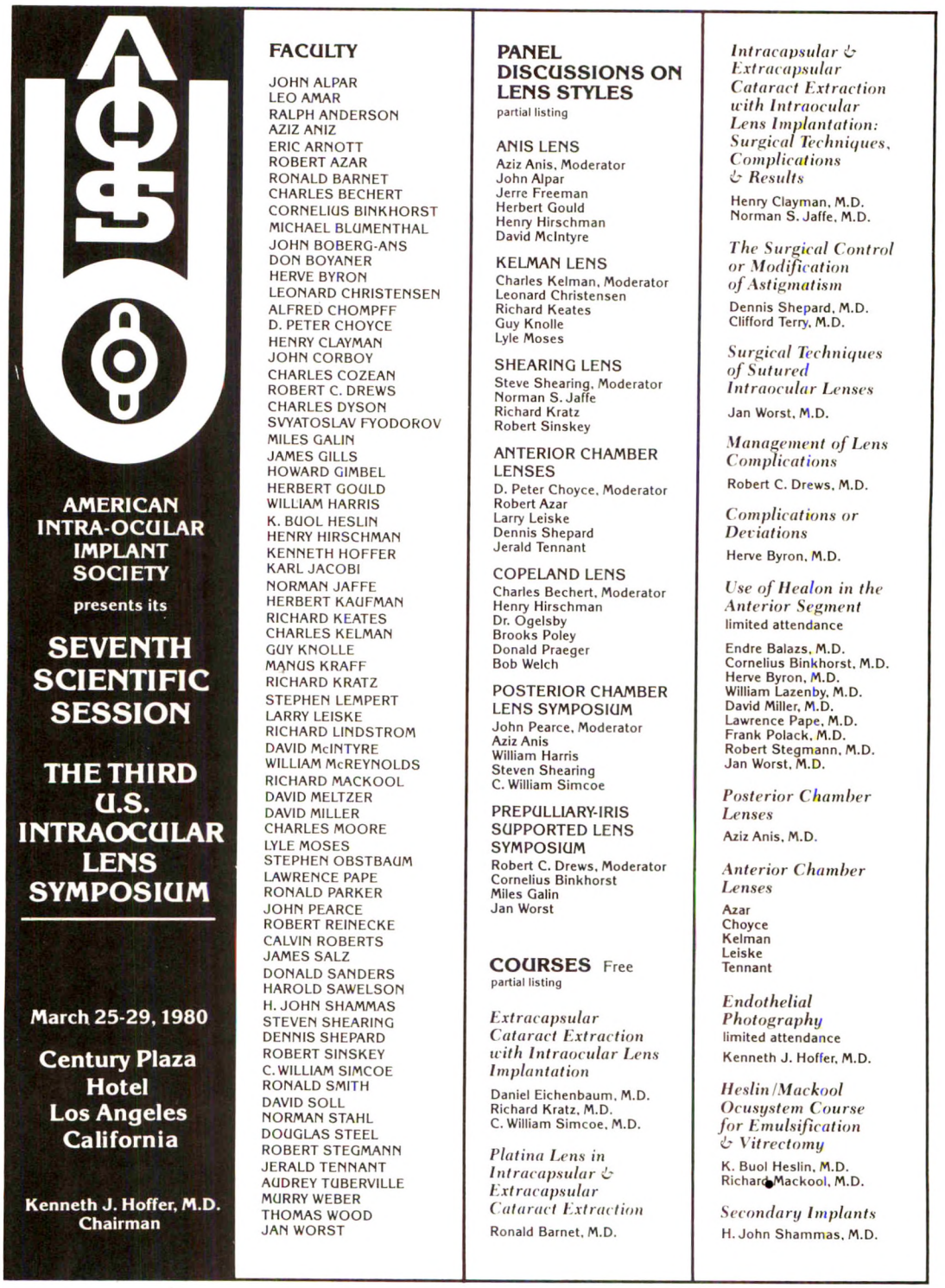

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PANEL DISCUSSIONS ON LENS STYLES

partial listing

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John Alpar
Jerre Freeman
Herbert Gould
Henry Hirschman
David McIntyre

KELMAN LENS

Charles Kelman, Moderator
Leonard Christensen
Richard Keates
Guy Knolle
Lyle Moses

SHEARING LENS

Steve Shearing, Moderator
Norman S. Jaffe
Richard Kratz
Robert Sinskey

ANTERIOR CHAMBER LENSES

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C. William Simcoe, M.D.

Platina Lens in Intracapsular & Extracapsular Cataract Extraction

Ronald Barnet, M.D.

Intracapsular & Extracapsular Cataract Extraction with Intraocular Lens Implantation: Surgical Techniques, Complications & Results

Henry Clayman, M.D.
Norman S. Jaffe, M.D.

The Surgical Control or Modification of Astigmatism

Dennis Shepard, M.D.
Clifford Terry, M.D.

Surgical Techniques of Sutured Intraocular Lenses

Jan Worst, M.D.

Management of Lens Complications

Robert C. Drews, M.D.

Complications or Deviations

Herve Byron, M.D.

Use of Healon in the Anterior Segment

limited attendance

Endre Balazs, M.D.
Cornelius Binkhorst, M.D.
Herve Byron, M.D.
William Lazenby, M.D.
David Miller, M.D.
Lawrence Pape, M.D.
Frank Polack, M.D.
Robert Stegmann, M.D.
Jan Worst, M.D.

Posterior Chamber Lenses

Aziz Anis, M.D.

Anterior Chamber Lenses

Azar
Choyce
Kelman
Leiske
Tennant

Endothelial Photography

limited attendance

Kenneth J. Hoffer, M.D.

Heslin/Mackool Ocusystem Course for Emulsification & Vitrectomy

K. Buol Heslin, M.D.
Richard Mackool, M.D.

Secondary Implants

H. John Shammas, M.D.

NURSES' AND TECHNICIANS' PROGRAM

Material to familiarize allied health personnel with the latest in intraocular surgery

Wednesday, March 26

Surgery Techniques

Intracapsular
Miles Galin, M.D.

Extracapsular
David McIntyre, M.D.

Phacoemulsification
Charles Kelman, M.D.

Vitrectomy
K. Buol Heslin, M.D.

Doing the Doctor's Paperwork
Dennis Shepard, M.D.

Eye Anatomy
Stephen Obstbaum, M.D.

Pre-Op Evaluation & History
Henry Clayman, M.D.

Lens Calculation
John Shammas, M.D.

Endothelial Photography
Manus Kraff, M.D.

Panel Discussion/ Question & Answer Period
Manus Kraff, M.D.
Moderator

Friday, March 28

Post-Operative Complications – Immediate & Future Treatment
Richard Kratz, M.D.

Post-Operative Care & Instruction
Murry Weber, M.D.

Psychological Needs of the Post-Op Patient
John Alpar, M.D.

Secondary Implants
John Darin, M.D.

Indications/ Contraindications
Norman Jaffe, M.D.

Surgical Complications
C. William Simcoe, M.D.

Panel Discussion/ Question & Answer Period
Norman Jaffe, M.D.
Moderator

GRAND BALL!

LADIES' PROGRAM!

An exciting Ladies' Program is planned, with a gourmet lunch and international fashion show at Beverly Hills' renowned Bistro restaurant; a thrilling tour of Universal Film Studio; a visit to beautiful Huntington Library, Art Gallery and Gardens with lunch at Emily's; live theater at Hollywood's famed Pantages... and much, much more! A definite must!

AMA Category I
40 hours

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REGISTRATION- U.S. INTRAOCULAR LENS SYMPOSIUM

Prior to Feb. 20: ☐ Members, Fellows and Military of AIOIS $375 ☐ Ladies' Program $156
☐ Non-Members $450 ☐ Residents $225 ☐ Nurses $150* ☐ Technicians $150*
☐ Use of Healon in the Anterior Segment Course ☐ Endothelial Photography Course

After Feb. 20: ☐ Members, Fellows and Military of AIOIS $425 ☐ Ladies' Program $181
☐ Non-Members $500 ☐ Residents $275 ☐ Nurses $175* ☐ Technicians $175*
☐ Use of Healon in the Anterior Segment Course ☐ Endothelial Photography Course

☐ Check here if you wish further information on the Ladies' Program

*Nurses' and technicians' fee includes attendance at general sessions, lunches, etc., as well as special Nurses' and Technicians' Course.

Each Registrant must fill out a separate form. Concellations: 90% refund prior to postmark date of Feb. 20. 10% refund after postmark date of Feb. 20. Residents must have a letter from Chief of Department. Make check or money order payable to U.S. Intraocular Lens Symposium and send with this form to P.O. Box 3140, Santa Monica, California 90403. For hotel reservations, please contact Century Plaza Hotel directly at Avenue of the Stars, Los Angeles, California 90067. Telephone (213) 277-2000. Toll free reservation number (213) 228-3000. When making reservations please indicate that you are with the AIOIS.

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A Chemical Sunglass

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Ninety-eight percent infrared and total ultraviolet are absorbed by the NoIR lenses. This selective transmission of light enhances vision and comfort as the eye receives only low levels of visible light necessary for vision.

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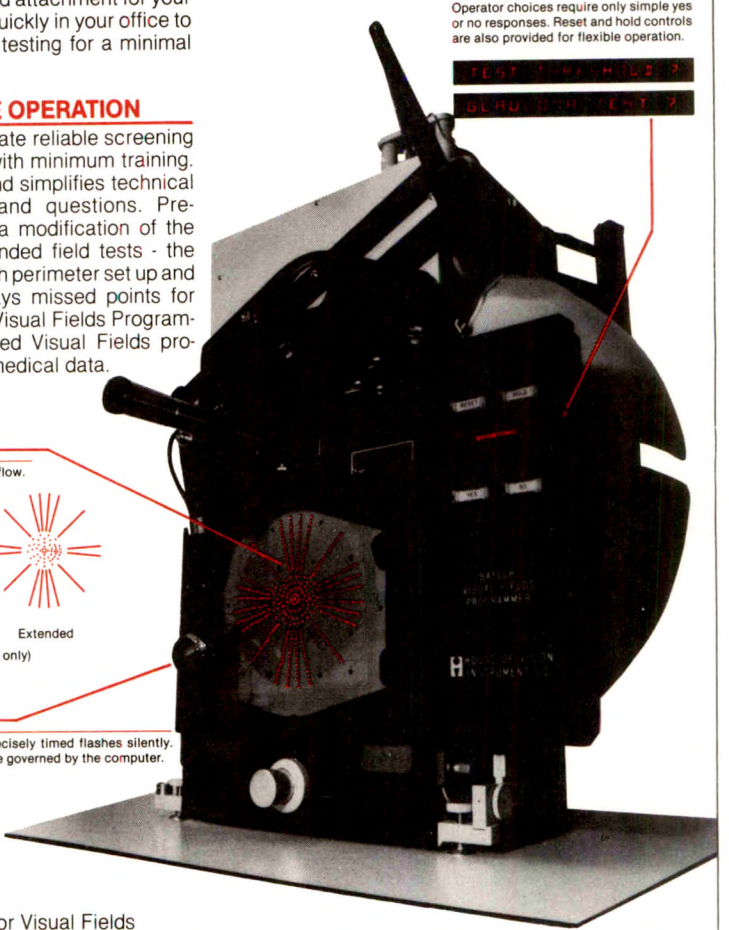

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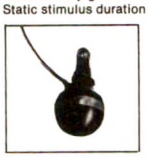

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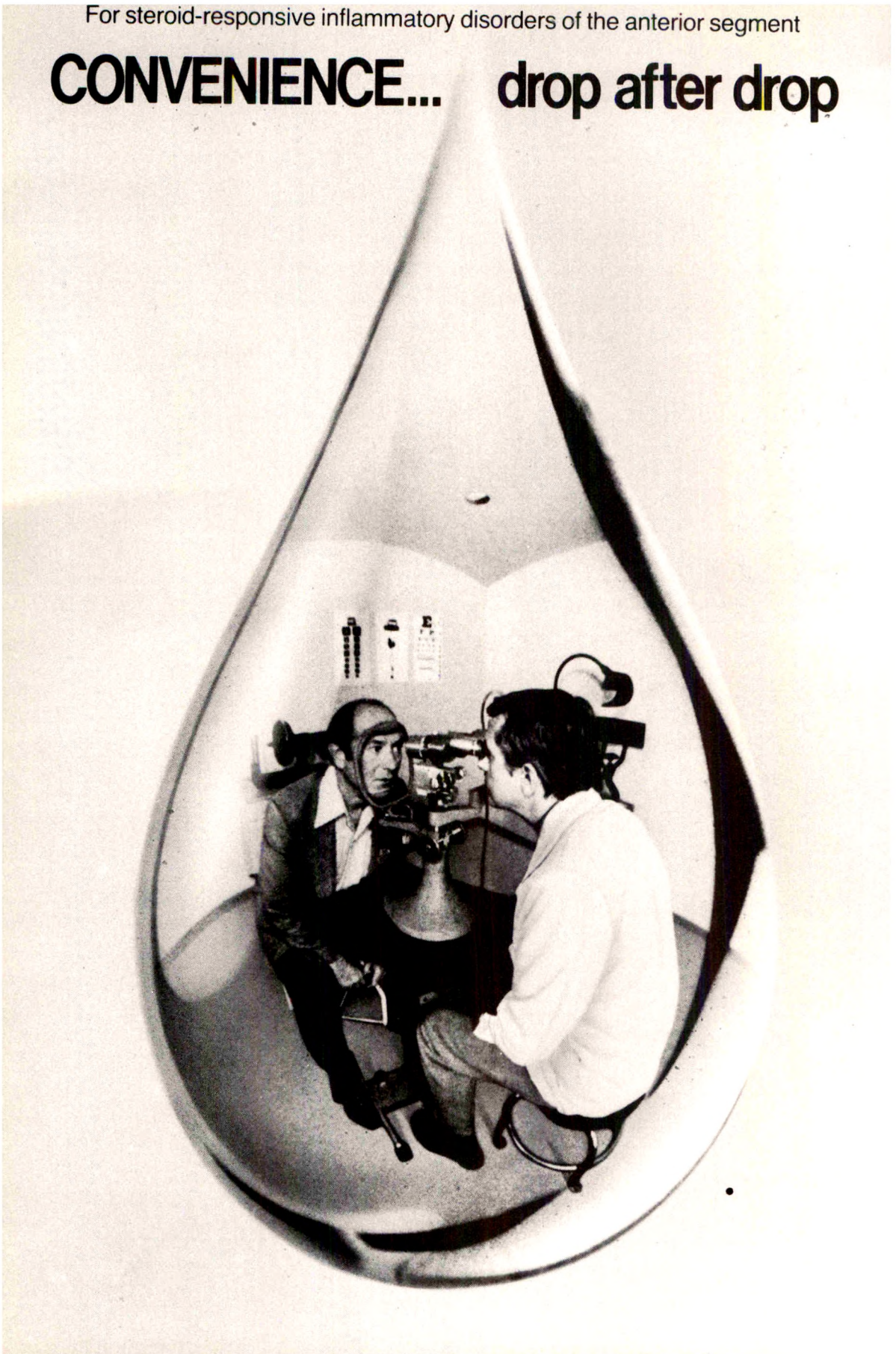

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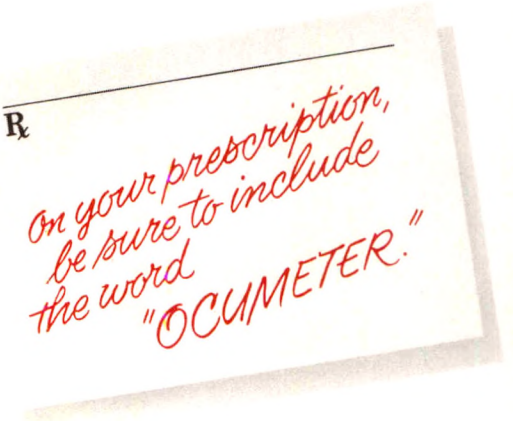

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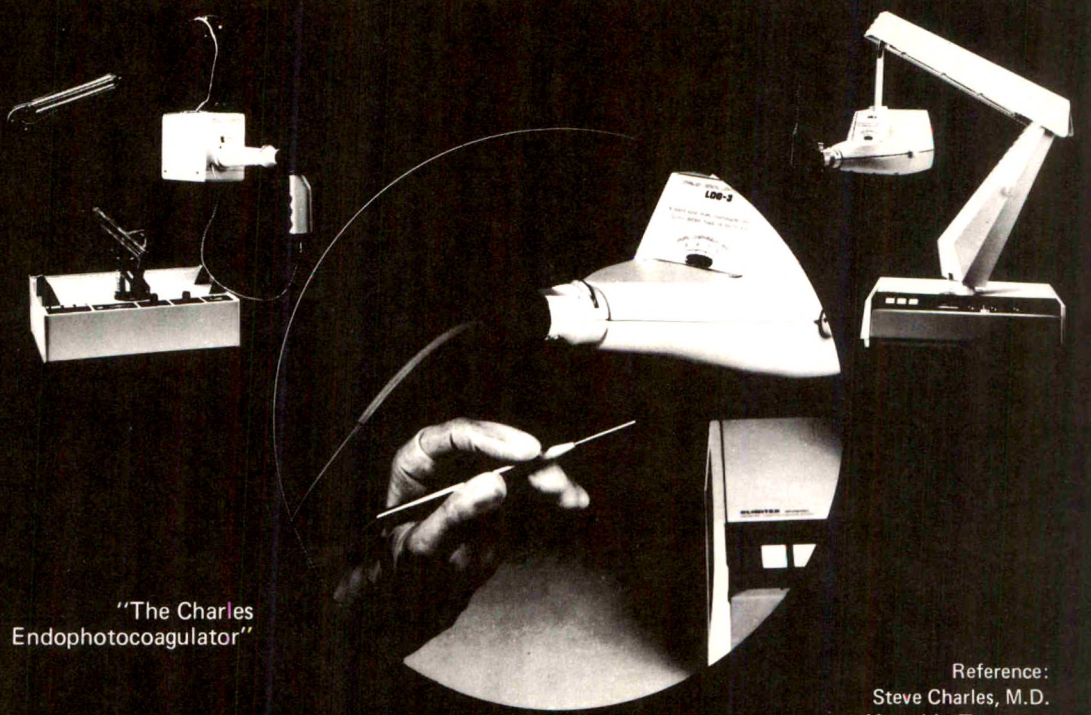

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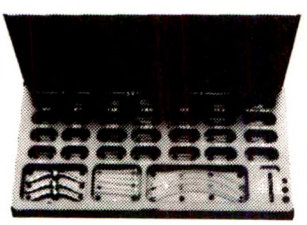
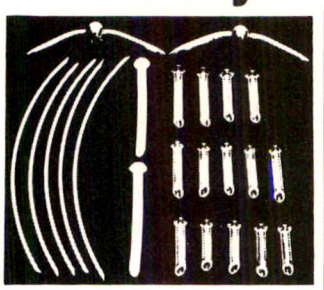
This anodized aluminum scale now gives you a fast way of measuring tubes for go-no go dimensions.



Sterilization Tray
Constructed of specially anodized aluminum, this impact-resistant tray protects your tubes as well as providing a convenient way of sterilization and handling...with enough pockets to hold all tubes from the three Jones Tube Sets.



Tear Duct Tubes
Complete L.T. Jones M.D. 2.2mm Diameter Sets are readily available in standard, assorted or special sets. Special sizes may be obtained upon request.

* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
L.T. Jones M.D. and J.L. Wobig M.D., Surgery of the Eyelids and Lacrimal System, Aesculapius Publishing Company, 1976.

Additional Information Available From:

Weiss *Scientific Glass Blowing Co.*

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Miniphage: 1.05mm Diameter With Built in Infusion

The DKS Miniphage is still the only miniature cutting head that offers infusion built in, not added on. The 1.05mm, diameter tip is a disposable, sharp and versatile cutting instrument guaranteed every time.

Two models are available: The V3001-120,with finger hole control of suction; and the V3001-124, with foot switch control of suction and positive shut-off.

Use of the V3001-124 will require modification to existing systems in the field. New systems are available with or without modification.

Available for December delivery in the new DKS disposable sterile pack.

One of a family of DKS precision disposable surgical instruments.

A product of David Kopf Instruments
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Peyman/Vitrophage

DKS

Ready When You Are

Bausch & Lomb Scientific Update:

Now, low plus
come of

Now Bausch & Lomb SOFLENS® (polymacon) low plus lenses offer better vision care for your hyperopic and presbyopic patients.

In the past, low plus lenses have been limited in performance. Now this has changed.

Bausch & Lomb Low Plus Lenses have been improved to offer you these important new features:

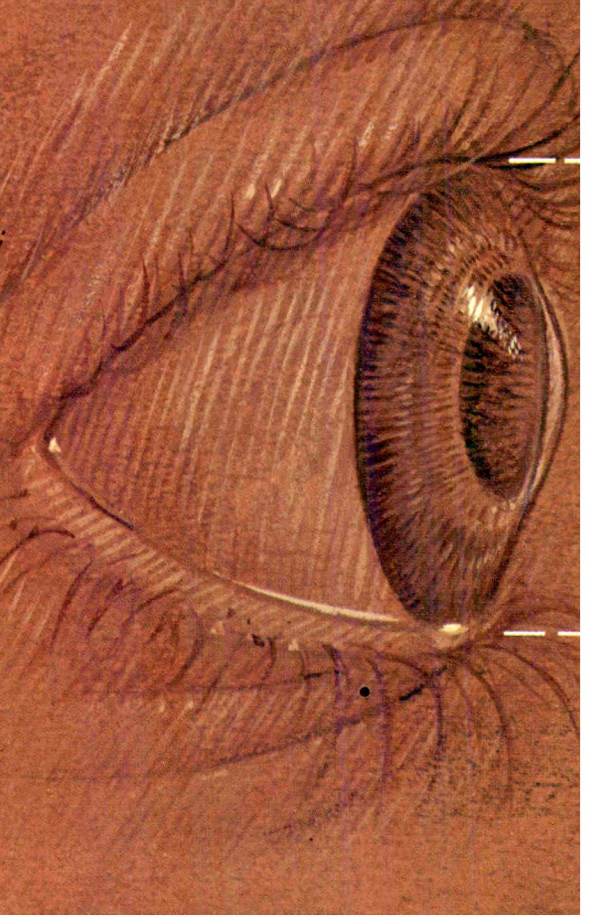
- *Three diameters – A greater range of fitting variables permitting the use of the First Fit system.*
  12.5mm +N Series
  13.5mm +B3 Series
  14.5mm +B4 Series
- *Larger Optical Zones – 9.0mm for the +B3; 10.0mm for the +B4.*
- *Reduced Center Thickness – Thinner than the older +F3 Series, power for power.*
- *Improved Clinical Performance* – In a clinical study of forty eyes, most patients wearing the new +B3 and +B4 Series demonstrated visual acuity better than or equal to spherical spectacle refraction, greater comfort, and improved lens positioning.*

Now with three diameters you'll be able to fit more patients than ever before with Bausch & Lomb Low Plus Lenses while offering better acuity and greater comfort.

Now the addition of two new low plus ser (13.5mm and 14.5mm) in powers fr +0.25 to +7.00D greatly expands y fitting opportunities.

Now the highly acceptable FIRST F method which has proven to be so success for fitting Bausch & Lomb minus lenses equally applicable for our new low p lenses.

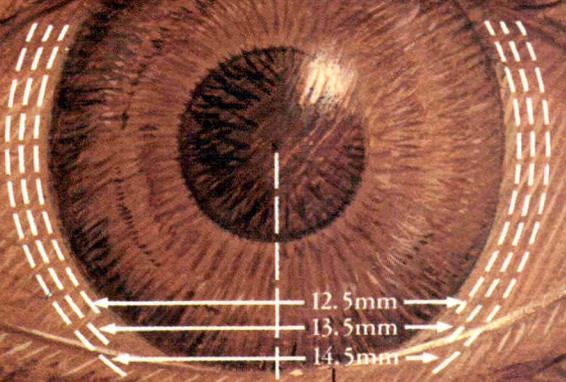
Now you can offer your hyperopic a presbyopic patients the same high quali and performance your myopic patien receive with Bausch & Lomb minus lens



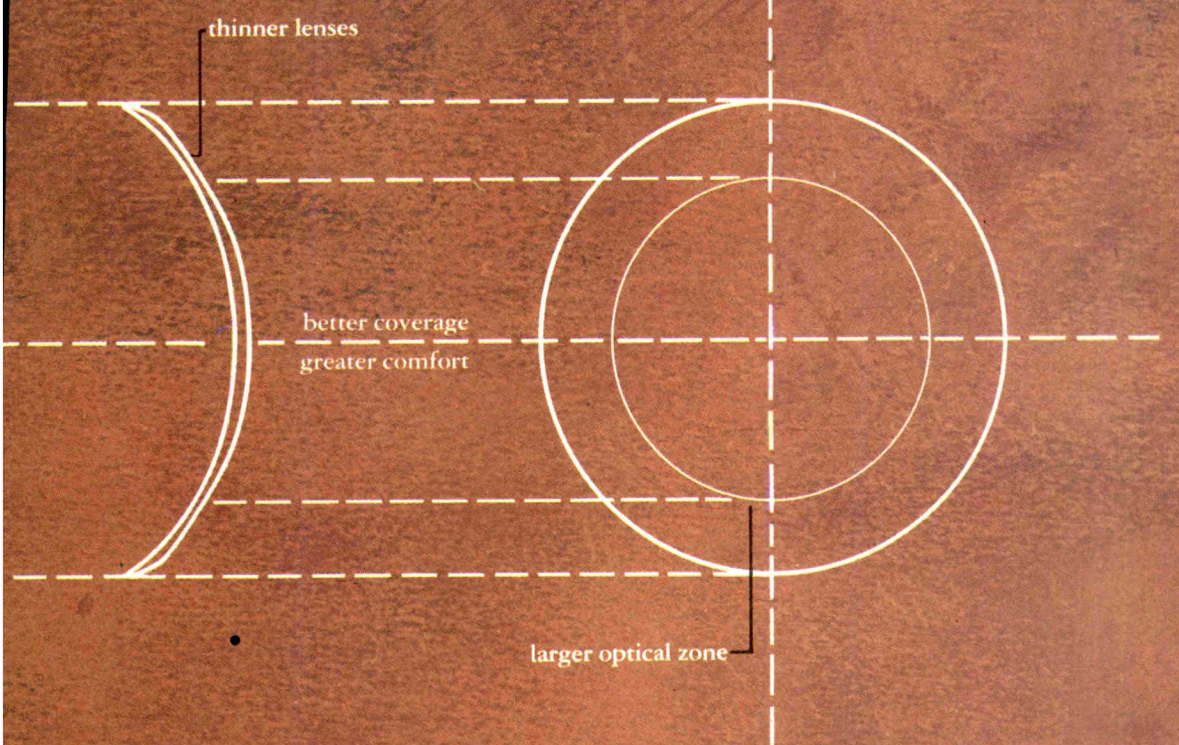
*Data on file at Bausch & Lomb.

lenses age!

mproved Low Plus Lenses . . . just ne of the ways Bausch & Lomb ffers you and your patients igh-quality ision care.



BAUSCH & LOMB
SOFLENS®
(polymacon)
Contact Lenses
The best that science and technology can provide.



See next page for brief summary of prescribing information.

BAUSCH & LOMB SOFLENS® (polymacon) Contact Lenses

BRIEF SUMMARY (For full prescribing information see package circular.)
VISION CORRECTION USE

INDICATIONS: SOFLENS® (polymacon) Contact Lenses are indicated for vision correction use in persons with non-diseased eyes and in aphakia. **CONTRAINDICATIONS:** SOFLENS® (polymacon) Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia and aphakia. **WARNINGS: Abrasions and Infections**—If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrent with lens wear, the lens should be removed immediately and a physician consulted. Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses. **Aphakic Patients**—Aphakic patients should not be fitted with SOFLENS® (polymacon) Contact Lenses during the postoperative period until, in the opinion of the surgeon, the eye has healed completely. **Lens Sanitation and Handling**—Persons who require only vision correction and who would not, or could not, adhere to the recommended daily-sanitary care of SOFLENS® (polymacon) Contact Lenses or who are unable to place and remove the lenses should not be provided with them. Failure to follow handling and sanitation instructions could lead to serious eye infections which might result in corneal ulcers. Malfunction and rusting of the metal interior of the BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure. Keep the BAUSCH & LOMB® Disinfecting Unit I (ASEPTOR®) clean and dry at all times. **Medicants and Eye Drops**—When the lenses are used by persons requiring only vision correction no ophthalmic solutions or medicants, including conventional (hard) contact lens solutions and eye drops, except BAUSCH & LOMB™ Lens Lubricant should be used by SOFLENS® (polymacon) Contact Lens wearers prior to placement, or while the lens is in place on the eye. Also, no solutions, including conventional (hard) contact lens solutions other than daily cleaner, lens lubricant, saline, and the solution made from the SOFLENS® Enzymatic Contact Lens Cleaning Tablets are to be used on a SOFLENS® (polymacon) Contact Lens when the lens is off the eye. **Wearing Restrictions**—SOFLENS® (polymacon) Contact Lenses, when used only for vision correction, should be removed before sleeping or swimming and in the presence of noxious and irritating vapors. Insufficient lacrimal secretions or hypoesthesia may be restricting factors to the wearing of soft contact lenses. **PRECAUTIONS: Storage**—SOFLENS® (polymacon) Contact Lenses must be stored ONLY in saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in saline solution until it returns to its soft, pliable state which may take as long as forty minutes. Fresh saline solution must be used DAILY for cleaning, storing, and disinfection of lenses. The carrying case must be emptied and refilled with fresh saline solution just before disinfecting the lenses. If using BAUSCH & LOMB™ Salt Tablets to make saline solution, the solution **MUST BE PREPARED FRESH DAILY.** As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected, or Preserved Saline Solution may be used. **Hygiene**—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses. Cosmetics, lotions, soaps, and creams must not come in contact with the lenses, since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled. **Handling**—A SOFLENS® (polymacon) Contact Lens may be damaged by nicking or tearing if care is not exercised during placement on or removal from the eye, replacing or removing it from the carrying case or in the cleaning process. Lenses must be placed very carefully in the carrying case to avoid damaging the edges of the lenses. **Disinfecting**—Fresh saline solution must be used DAILY for cleaning, storing and disinfection of lenses. If using BAUSCH & LOMB™ Salt Tablets to make saline solution, the solution **MUST BE PREPARED FRESH DAILY.** After removal from the eye, the SOFLENS® (polymacon) Contact Lens must be rubbed gently with Daily Cleaner then rinsed with saline solution to remove mucus and film from the lens surface. The BAUSCH & LOMB® Lens Carrying Case (LENSGARD®) must be emptied and refilled with fresh saline solution just before disinfecting the lenses. In order to remove protein deposits which may form on the lenses, wearers should use the SOFLENS® Enzymatic Contact Lens Cleaning Tablets according to the directions for use which accompany the tablets. To help remove tear residues and mucus as well as other deposits that tend to accumulate on the lens surface, patients should use Daily Cleaner according to the directions for use which accompany the product. Disinfecting with a BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) or II (ASEPTRON®) is necessary to kill microorganisms. If a BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) or II (ASEPTRON®) is not available, the lenses may be disinfected by boiling them in their carrying case in a pan of water for ten minutes. When this boiling method of disinfection is used, the lenses can be damaged if the boiling water is allowed to completely evaporate. The BAUSCH & LOMB® Lens Carrying Case (LENSGARD®) must **always** be **⅔ full** of fresh saline solution before disinfecting and must **always** be tightly closed to prevent leakage of the saline from the case and subsequent dehydration of the lenses. **Fluorescein**—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with sterile normal saline solution and wait at least one hour before replacing the lenses. Earlier replacement may cause the lenses to absorb residual fluorescein. **ADVERSE REACTIONS:** Serious corneal damage may result from wearing a SOFLENS® (polymacon) Contact Lens which has been soaked in a conventional contact lens solution. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation. A lens adheres very rarely to an eye as a result of sleeping with the lens on, or wearing a hypotonic lens. If a lens adheres for any reason, apply fresh saline and wait until the lens moves freely before removing it. Clinical studies indicate that corneal edema, as manifested by symptoms such as rainbows, halos around lights, or foggy vision, may occur in less than 5% of SOFLENS® (polymacon) Contact Lens wearers. If these symptoms occur, the lenses should be removed and professional consultation obtained. Excessive tearing, unusual eye secretions, and photophobia are not normal. If these symptoms occur, the patient should be examined to determine their cause. A faint blue haze, believed to be located in Descemet's membrane, has been reported in the Spokane, Washington area. As yet, the cause is unknown and the phenomenon has not been found elsewhere. The wearers report no subjective symptoms and there is no detectable effect on their visual acuity. There have been approximately 29 cases, and in 10 of these patients the blue haze has cleared or is in various stages of regression. Neovascularization of the cornea has been observed in some aphakic patients fitted with the SOFLENS® (polymacon) Contact Lens, which may require discontinuation of the lens. Medical consultation should be obtained in such an instance.

October 1979

BAUSCH & LOMB
SOFLENS DIVISION
Rochester, New York 14602

GARAMYCIN®
brand of
gentamicin sulfate, U.S.P.
OPHTHALMIC
Solution-Sterile
Ointment-Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci; and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species, including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

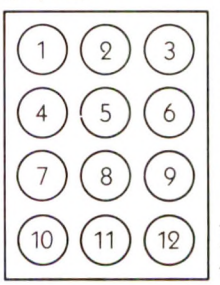
GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube, boxes of one and six. Store away from heat.

NOVEMBER 1973 10089900

For complete details, consult package insert or literature available from your Schering Representative, or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.



1. Staphylococcus sp.
2. Streptococcus sp.
3. H. influenzae
4. H. aegyptius
5. M. lacunata
6. Neisseria sp.
7. Proteus sp.
8. P. aeruginosa (certain strains)
9. E. coli
10. A. aerogenes
11. K. pneumoniae
12. D. pneumoniae

Schering
Schering Corporation
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SWW 1320 RI

Solution–Sterile/Ointment–Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

Schering

GARAMYCIN® OPHTHALMIC

d of

entamicin sulfate, U.S.P.

STANDS THE TEST OF TIME THROUGHOUT A BROAD RANGE OF OCULAR INFECTIONS*

e to susceptible organisms. In vitro
ta is not necessarily indicative of
nical effectiveness. Sensitivity data
y vary among institutions and
y depend on the technique used
sensitivity testing.

ease see adjacent product
ormation.

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VIRA-A®
(vidarabine ophthalmic ointment), 3%

Description. Vira-A (vidarabine, adenine arabinoside, or Ara-A) is an antiviral drug for topical ophthalmic administration. The chemical name is 9-β-D-arabinofuranosyladenine. Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

Clinical Pharmacology. Vira-A is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Except for Rhabdovirus and Oncornavirus, Vira-A does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

The antiviral mechanism of action has not been established. Vira-A appears to interfere with the early steps of viral DNA synthesis. Vira-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of Vira-A. Because of the low solubility of Vira-A, trace amounts of both Vira-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of Vira-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, Vira-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, Vira-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit.

Indications and Usage. Vira-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. Vira-A is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions to idoxuridine have occurred. The effectiveness of Vira-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous Vira-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone, have been administered concurrently with Vira-A Ophthalmic Ointment, 3%, without an increase in adverse reactions.

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If Vira-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

Vira-A is not effective against RNA virus or adenoviral ocular infections. Vira-A is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Contraindication. Vira-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. ***Use in Pregnancy:*** Vira-A (vidarabine) parenterally is teratogenic in rats and rabbits. Ten percent Vira-A ointment applied to 10% of the body surface during organogenesis induc fetal abnormalities in rabbits. When 10% Vira-A ointment was plied to 2 to 3% of the body surface of rabbits, no fetal abn malities were found. This dose greatly exceeds the total recc mended ophthalmic dose in humans. The possibility of embryo or fetal damage in pregnant women receiving Vira-A (vidarab ophthalmic ointment), 3%, is remote. The topical ophthalmic dc is small, and the drug relatively insoluble. Its ocular penetratior very low. However, a safe dose for a human embryo or fetus h not been established. Consequently, Vira-A should be used o when clearly indicated.

It is not known whether Vira-A is excreted in human milk. As general rule, because many drugs are excreted in human m nursing should not be undertaken while a patient is under tre ment. However, excretion of vidarabine in breast milk is unlike because Vira-A is rapidly deaminated in the gastrointestinal tra

Mutagenic Potential: Results of *in vitro* experiments indica that vidarabine can be incorporated into mammalian DNA and c induce mutation in mammalian cells (mouse L5178Y cell lin Thus far, *in vivo* studies have not been as conclusive, but there some evidence (dominant lethal assay in mice) that vidarabi may be capable of producing mutagenic effects in male ger cells.

It has also been reported that vidarabine causes chromoson breaks and gaps when added to human leukocytes *in vitro*. Wh the significance of these effects in terms of mutagenicity is n fully understood, there is a well-known correlation between t ability of various agents to produce such effects and their abili to produce heritable genetic damage.

Oncogenic Potential: Chronic parenteral (IM) studies vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant i crease in liver tumor incidence among the vidarabine-treat females. In the same study, some vidarabine-treated male mi developed kidney neoplasia. No renal tumors were found in t vehicle-treated control mice or the vidarabine-treated fema mice.

In the rat study, intestinal, testicular, and thyroid neoplasia o curred with greater frequency among the vidarabine-treat animals than in the vehicle-treated controls. The increases thyroid adenoma incidence in the high-dose (50 mg/kg) mal and the low-dose (30 mg/kg) females were statistically signi cant.

Hepatic megalocytosis, associated with vidarabine treatmer has been found in short- and long-term rodent (rat and mous studies. It is not clear whether or not this represents a pr neoplastic change.

The recommended frequency and duration of administratic should not be exceeded (see Dosage and Administration).

Precautions. The diagnosis of keratoconjunctivitis due to Herpe simplex virus should be established clinically prior to prescribir Vira-A Ophthalmic Ointment, 3%.

Patients should be forewarned that Vira-A Ophthalmic Oir ment, 3%, like any ophthalmic ointment, may produce a tempora visual haze.

Although viral resistance to Vira-A has not been observed, th possibility may exist.

Adverse Reactions. Lacrimation, foreign-body sensation, co junctival injection, burning, irritation, superficial puncta keratitis, pain, photophobia, punctal occlusion, and sensitivi have been reported with Vira-A Ophthalmic Ointment, 3%. Th following have also been reported but appear disease-relate uveitis, stromal edema, secondary glaucoma, trophic defects, co neal vascularization, and hyphema.

Overdosage. Acute massive overdosage by oral ingestion of th ophthalmic ointment has not occurred. However, the rap deamination to arabinosylhypoxanthine should preclude ar difficulty. The oral LD_{50} for vidarabine is greater than 5,020 m kg in mice and rats. No untoward effects should result from inge tion of the entire contents of a tube.

Overdosage by ocular instillation is unlikely because any e cess should be quickly expelled from the conjunctival sac. Tc frequent administration should be avoided.

Dosage and Administration. Administer approximately one ha inch of Vira-A Ophthalmic Ointment, 3%, into the lower co junctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or comple re-epithelialization has not occurred by 21 days, other forms therapy should be considered. Some severe cases may requi longer treatment.

After re-epithelialization has occurred, treatment for an adc tional seven days at a reduced dosage (such as twice daily) recommended in order to prevent recurrence.

How Supplied. N 0071-3677-07 (Stock 18-1677-139)

Vira-A Ophthalmic Ointment, 3%, is supplied sterile ophthalmic ointment tubes of 3.5 g. The base is a 60:40 mixtu of solid and liquid petrolatum. U

PARKE-DAVIS
Division of Warner-Lambert Compa
Morris Plains, NJ 07950

PD-JA-2320-1-P(5-78)

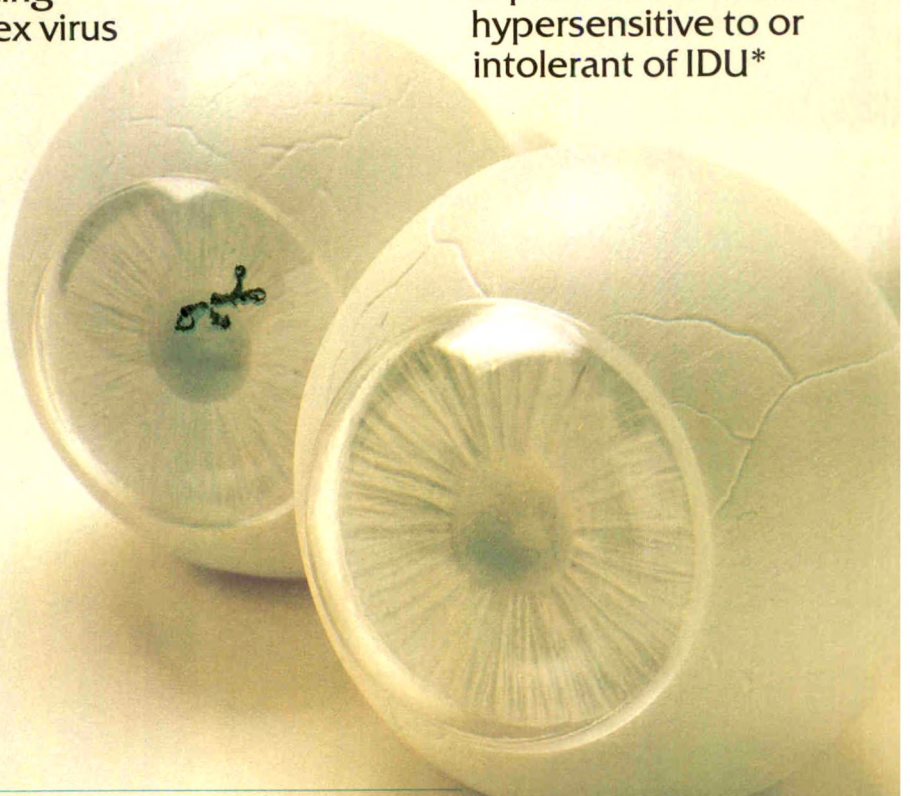
A LOGICAL FIRST CHOICE FOR HERPES SIMPLEX VIRUS KERATITIS

VIRA-A®

(vidarabine ophthalmic ointment), 3%

ot only as effective
s IDU in treating
erpes simplex virus
eratitis...

but is also effective in patients resistant or hypersensitive to or intolerant of IDU*



linical Evidence	No. of Subjects	Description	Effective Response
ira-A ontrolled Trials	81	Previously untreated	70 subjects **(86%)**
ira-A ncontrolled Trials	142 •	75% had been resistant or hypersensitive to IDU	101 subjects **(71%)**

IOTE: In the controlled and uncontrolled trials, 70 and 101 subjects, espectively, re-epithelialized at the end of three weeks on Vira-A.

ata on file, Medical Department, Parke-Davis.

Vira-A is preservative-free.

lease see prescribing information on preceding page.

PARKE-DAVIS

POLYCON®

(silafocon A) CONTACT LENS

Provides visual acuity, maintains normal corneal physiology

The POLYCON lens* is a rigid, oxygen-permeable contact lens with excellent stability. It is made from a copolymer containing silicon and methyl methacrylate (MMA).

Extensive clinical data demonstrate distinct benefits

418 patients completed a multiclinic study** with the following results:

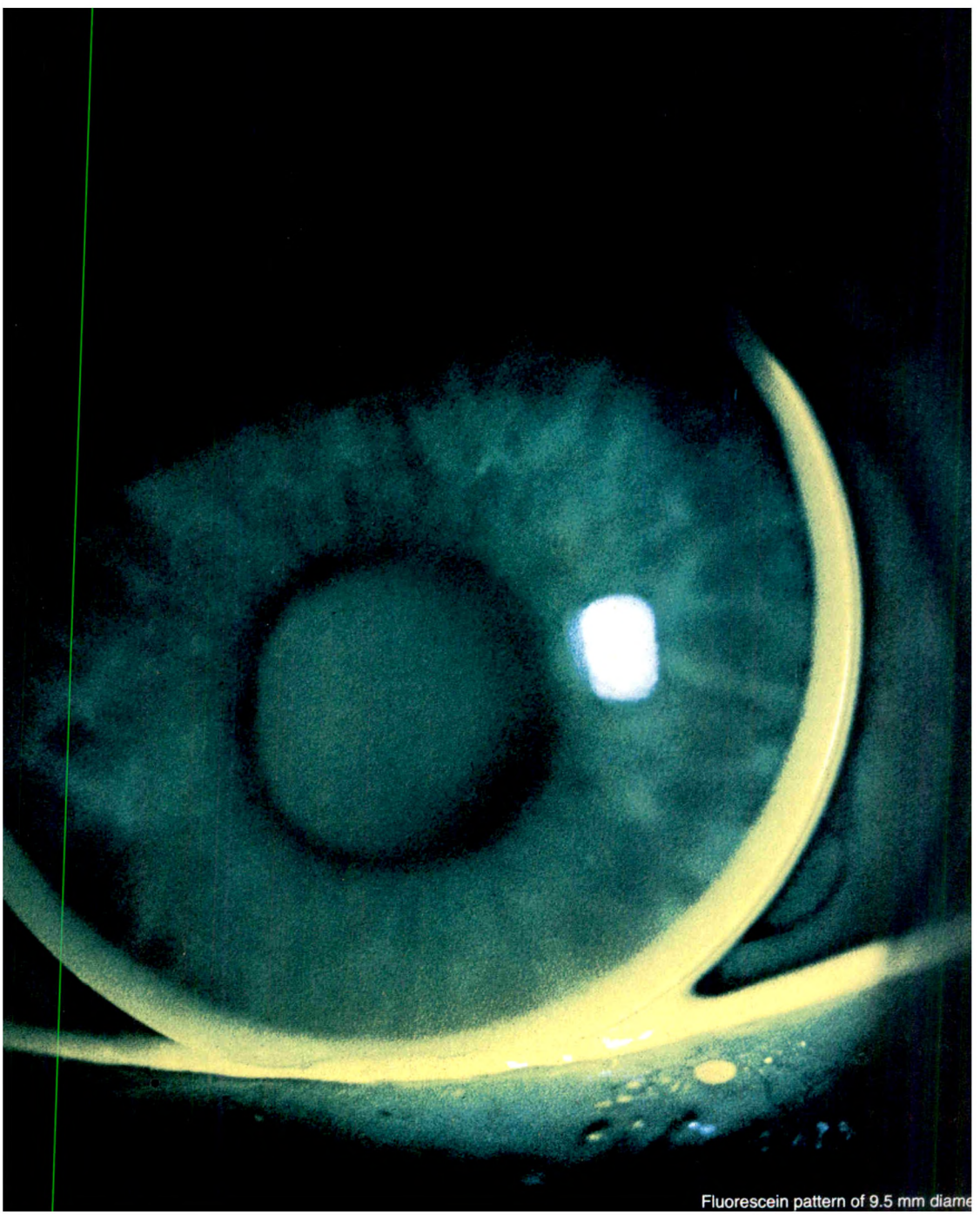
No edema reported in 96.4% of patient visits
No spectacle blur reported in 99.5% of patient visits
No flare or halo problems reported in 99% of patient visits
All-day comfort reported in 90% of patient visits

For more information, call toll-free (800) 528-0366 today; in Arizona, call collect (602) 242-6146.

Please see the third page of this advertisement for brief summary information.
**Data on file, Syntex Ophthalmics, Inc.

SYNTEX

SYNTEX OPHTHALMICS, INC.



Fluorescein pattern of 9.5 mm diame

POLYCON®
(silafocon A) CONTACT LENS

BRIEF SUMMARY

INDICATIONS
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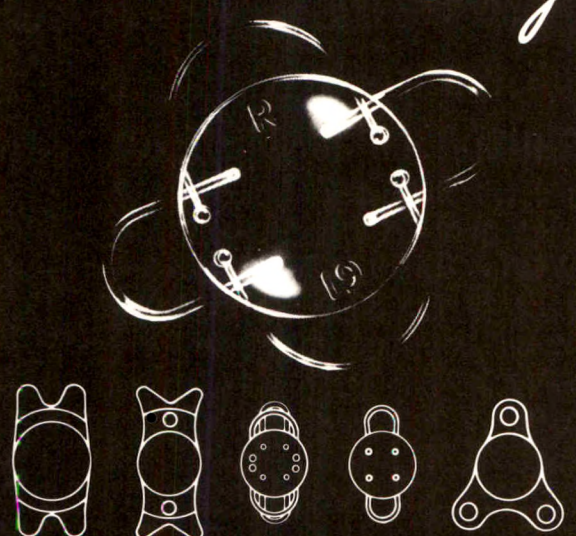

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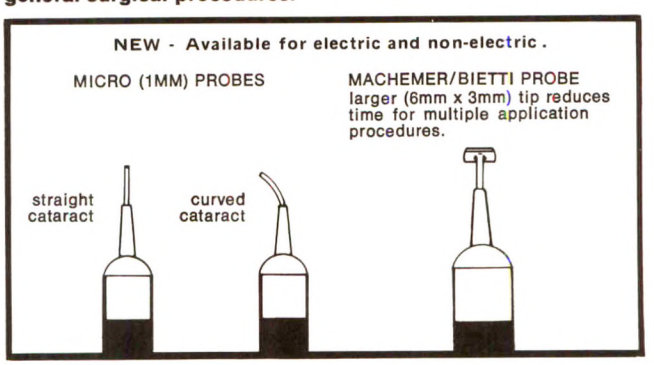

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CELLULAR IMMUNE RESPONSIVENESS OF UVEITIS PATIENTS TO RETINAL S-ANTIGEN

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The mechanisms of ocular inflammatory disease have been the subject of much speculation.[1,2] Cellular immunity is known to play an important role in laboratory models for uveitis,[3,4] and several studies have shown the participation of the cellular immune process in several clinical ocular entities as well.[5–8] For most, crude ocular antigen preparations were used, leaving in doubt the specific exciting agent.

A uveitogenic retinal agent has been speculated on for some time.[9–11] The soluble retinal antigen, or S-antigen, first purified separately by Wacker and Donoso[12] and Faure and associates[13] in 1975, is an efficient immunizing agent for the induction of uveitis in the laboratory. This material, with a molecular weight of approximately 50,000 daltons, has been purified from the photoreceptor region of bovine, human, rabbit, and guinea pig retinas. An immunizing dose as low as 5 μg of purified S-antigen injected at a distant site will provoke a severe ocular inflammatory response in most laboratory animals tested.[14] A clinical similarity is evident between the ocular inflammation seen after immunization with S-antigen and various ocular inflammatory conditions seen in man.

The blast transformation of lymphocytes in culture is considered to be the counterpart of the immune memory in vivo.[15,16] This method was used in this study to evaluate the response of lymphocytes from patients with ocular inflammatory disease when exposed to S-antigen and a variety of crude ocular antigen preparations. To the best of our knowledge, our results show for the first time the presence of cellular immune memory to a purified retinal antigen in patients with ocular inflammatory disease.

SUBJECTS AND METHODS

Patient selection—Peripheral blood samples were taken from 31 consecutive uveitis patients seen at the National Eye Institute; 21 of these patients had a disease process predominantly involving the posterior segment of their eyes. Additionally, blood samples were taken from nine

From the National Eye Institute, Clinical Branch (Drs. Nussenblatt and Ballintine), and Laboratory for Vision Research (Dr. Gery), National Institutes of Health, Bethesda, Maryland; and the Department of Ophthalmology (Dr. Wacker), University of Louisville, Louisville, Kentucky.

Reprint requests to Robert B. Nussenblatt, M.D., National Eye Institute, Clinical Branch, Building 10, Room 10N-313, 9000 Rockville Pike, Bethesda, MD 20205.

normal volunteers with no history of ocular inflammatory disease. All patients and volunteers received a thorough ocular examination with fluorescein angiography, fundus photographs, and visual field measurements performed when warranted.

Preparation of antigens—S-antigen was prepared as described elsewhere by Wacker and associates.[14] For this study, both bovine and human S-antigen were used. Human eyes were obtained at autopsy with dissection performed immediately. Crude preparations of choroid, retina, ciliary body, and iris were prepared as described elsewhere.[17] Aliquots of each preparation were kept at −20° C. Protein concentrations were determined by the Lowry method.[18]

Lymphocyte cultures—The mononuclear fraction was separated from blood by gradient centrifugation.[19] Rosewell Park Memorial Institute (RPMI) 1640 medium with HEPES supplemented with 2 mM of glutamine; penicillin, 100 units/ml; and streptomycin, 100 μg/ml, was used for all cell suspensions. Cultures were set up in triplicates or sextuplicates in microplates, and consisted of 2×10^5 lymphocytes per well, in 0.2 ml of medium with 10% heat inactivated human AB serum. All crude antigen preparations and the S-antigen were added in 10-μl aliquots. Purified S-antigen concentrations ranged from 1 to 25 μg/ml, and crude antigen concentrations from 50 to 100 μg/ml. Phytohemagglutinin-P was tested in each culture system. Control cultures were supplemented with 10 μl of medium per well. The cell cultures were incubated for 4-½ days at 37° C with 5% CO_2, pulsed for 14 hours with 1 μCi per well of tritiated thymidine, and harvested on a MASH II harvester. The incorporated radioactivity was measured by a Beckman scintillation counter. All results are expressed as Stimulation Index (S.I.), which is derived by dividing the mean counts per minute of tritiated thymidine in culture wells with antigen by the mean counts per minute in the culture wells without antigen. The mean counts differed from the individual cultures in each test group by less than 15%. An S.I. greater than 2.0 was taken as significant; this being the upper limit of the control sample tolerance limits. Tolerance limits of the control samples were found by the following formula: $\chi + \kappa \cdot S.D.$, with κ a table value of a proportion coverage of 90% and a confidence level of 90%.[20] Tolerance limits for the control group were thus calculated as being 1.2 ± 0.8.

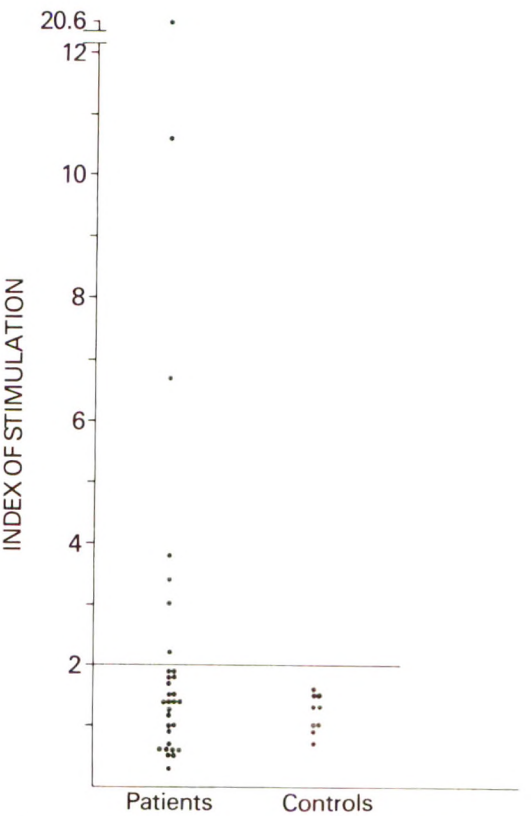

Figure (Nussenblatt and associates). Mitotic responses of patients and controls to bovine S-antigen.

RESULTS

Response to bovine S-antigen—Blood mononuclear cells from 31 patients and nine normal volunteers were tested for their mitotic responses to purified retinal soluble antigen (S-antigen), as well as to a variety of ocular tissue extracts.

The magnitudes of the lymphocyte responses, expressed as Stimulation Index values are shown in the Figure. Seven of the 31 patients reacted significantly with an S.I. above 2.0. All responders had disease processes primarily involving the posterior segment of the eye (Table 1).

A marked male preponderance was found in the responder group (Table 2). All responding patients had evidence of retinal inflammatory disease for at least two years before being tested. Six of the seven patients are known to have had at least two attacks, with three of them having a chronic "waxing and waning" course; five of the seven patients had an active uveitis when tested. Unusually high levels of response were found in patients with sarcoid and toxoplasmosis. All responders were tested at least twice to verify the response; in all cases responses approached the initial results.

TABLE 1

DISEASE ENTITIES INVESTIGATED

	S-Antigen Responders	S-Antigen Non-responders
Anterior uveitis	0	5
Ankylosing spondylitis	0	1
Still's disease	0	1
Mooren's ulcer	0	1
Pars planitis	1	2
Ocular sarcoid	1	1
Chorioretinitis of unknown origin	1	4
Presumed ocular histoplasmosis	0	2
Ocular toxoplasmosis	3	2
Behçet's disease	0	2
Chronic uveitis with macular disease	1	0
Vogt-Kayanagi-Harada's syndrome	0	1
Retinitis secondary to cryopexy	0	1
Optic neuritis	0	1

A comparison of responder and nonresponder groups shows that, besides the male preponderance, a higher percentage of patients in the responder group had inflammatory activity when tested (Table 3). Only 58% of the nonresponder

TABLE 2

S-ANTIGEN RESPONDER GROUP

Patient No., Sex, Age (yrs)	Medication	Activity	Ocular Disease	Onset	No. of Attacks	S.I.*
4, M, 64	Corticosteroid drops	Active	Chorioretinitis unknown origin	1976	Chronic	3.0
12, M, 69	Corticosteroid drops	Active	Chronic uveitis macula lesion	1976	3	3.4
13, M, 35	None	Inactive/ active	Toxoplasmosis/ syphilis	1949/ 1979	Unknown	2.2
18, M, 27	Systemic corticosteroids	Active	Toxoplasmosis panuveitis	1976	Chronic	6.7
22, M, 38	None	Inactive	Toxoplasmosis	1961	3	20.6
25, M, 36	None	Active	Sarcoid	1959	Chronic	10.6
31, F, 22	None	Active	Pars planitis	1977	2	3.8

*S.I. indicates Stimulation Index with S-antigen in culture.

TABLE 3

COMPARISON OF RESPONDER AND NONRESPONDER GROUPS

	Responders	Nonresponders
Average age	37 yrs	35.5 yrs
Range	(22-69 yrs)	(14-65 yrs)
Average duration	11.3 yrs	8.8 yrs
Range	(2-30 yrs)	(1-46 yrs)
Clinically active when tested	5/7 (71%)	10/24 (42%)
Male/Female	6/1	14/14
Racial distribution*	2B,1H,4W	3B,2H,19W
Retinal involvement	7/7	14/24
Taking systemic corticosteroids when tested	1/7	3/24

*B designates black; H, hispanic; and W, white.

TABLE 4

COMPARISON OF MITOTIC RESPONSES TO HUMAN AND BOVINE S-ANTIGEN

Patient No.	Human S-antigen	Bovine S-antigen
2	1.4*	1.8
9	0.4	1.3
12	5.4	3.4
13	1.7	2.2
18	5.0	10.6
22	12.4	20.6
24	0.9	0.6
28	1.1	1.0
31	2.2	3.8
Responders	4/9	5/9

*Stimulation Index.

group showed evidence of retinal involvement.

Response to human S-antigen in culture—The mitotic responses of lymphocytes from nine of the 31 patients were simultaneously studied with human and bovine S-antigen. Though less is known about human S-antigen, it is similar in molecular weight and its reactivity to guinea pig anti-S anti-sera parallels that of other better known S-antigen preparations (unpublished data, 1978).

A good correlation of response between human and bovine S-antigens was evident (Table 4). None of those in the nonresponder group to bovine S-antigen were responders to human S-antigen. One patient's response to human S-antigen was higher than his response to bovine.

Response to crude ocular antigen preparation—Crude ocular antigen preparations were used in each series of cultures. These included human choroid, retina, iris, ciliary body, and lens. Of these preparations, only retina yielded a significant response from lymphocytes in culture. Three of seven patients who responded to bovine S-antigen showed a significant response to retina (Table 5). Additionally, two patients with retinal involvement gave responses that were significant when crude retinal preparations were used, but were not significant when S-antigen was placed in culture. No correlation was seen between bovine S-antigen responses and the response to heat inactivated fetal calf serum, which were tested simultaneously in all patients. Additionally, the mitogen phytohemag-

TABLE 5

RESPONSIVENESS TO S-ANTIGEN AND HUMAN RETINAL EXTRACT*

Patient No.	Bovine S-antigen	Human Retinal Extract
S-antigen responder group		
22	20.6†	1.8
31	3.8	1.8
13	2.2	1.0
18	10.6	1.0
12	3.4	2.7
4	3.0	4.5
25	6.7	3.4
S-antigen nonresponder group		
5	1.4	2.0
14	1.4	4.0

*Table includes all S-antigen responders and those responders who reacted to human retinal extract; all other patients manifested Stimulation Indices below 2.0.

†Stimulation Index.

glutinin-P was used in all culture systems as a means by which lymphocyte responsiveness could be assessed. Both the control and patient groups responded in a similar fashion.

Discussion

The retinal soluble antigen (S-antigen) is a highly uveitogenic organ-specific antigen isolated from the retina of several mammalian species. Work in our laboratory has indicated that S-antigen immunized animals with evidence of ocular inflammation show an excellent cellular immune response when their lymphocytes are tested with this antigen in culture (unpublished data). Patients with a wide variety of ocular inflammatory diseases were thus studied in order to assess whether immune recognition of the S-antigen could be elicited. By using the microculture technique, purified as well as crude ocular antigen preparations could be simultaneously tested in the same system.

A subpopulation of the patients studied (22%) whose lymphocytes manifested a positive response to S-antigen could be defined. These patients all had retinal involvement associated with their disease. A comparison of the duration of the disease as well as numbers of attacks did not reveal significant differences between the responder and nonresponder groups. A marked preponderance of males in the responder group was seen. No patients were studied at the onset of their disease, and therefore no comment can be made as to how early evidence of immune memory occurs.

The similarity between the responses to human and bovine S-antigen tested simultaneously indicates that the purified bovine antigen can be used in future human studies. Of the crude ocular preparations tested, only retina provoked a significant immune response from patients' lymphocytes tested. These results support the greater antigenicity of the retina as opposed to the choroid as had been previously reported by others.[21–23] Though choroid may have an immunostimulatory potential, part of the immunologic properties of the choroid may possibly be the result of retinal products or specifically the pigment epithelial layer. Faure and associates[24] have reported that the immunopathogenic activity of the choroid is markedly reduced with the removal of the pigment epithelium.

The finding in two patients of posterior uveitis and positive responses to crude retinal preparations but not to S-antigen would strongly suggest the presence of other retinal antigens that may be the inciting immunologic cause. One of us[25] has already described a retinal as well as a choroidal antigen that may also be uveitogenic.

In the S-antigen responder group, significant stimulation indices were found in four patients whose lymphocytes responded to purified human or bovine S-antigens, or both, but not to crude human retina extract. This anomaly may be the result of partial masking of S-antigen in crude extracts by formation of complexes with other molecules or inhibitors, which are removed during purification of the antigen. Supporting this suggestion, bovine S-antigen in crude extracts is only slightly pathogenic for the guinea pig, if at all, but shows a striking increase in pathogenicity with each step of purification.[14] A similar situation has also been observed for the pathogenicity of homologous S-antigen in the rabbit (unpublished data). Partial masking of S-antigen may thus interfere with both immunogenic stimulation and immunologic recognition.

High S.I.'s (10.6, 20.6) were found when purified S-antigen was used in lymphocyte cultures from some patients.

Similarly, high responses were also found by Ehrenfeld, Klein, and BenEzra[26] in several patients with Hashimoto's disease when their lymphocytes were cultured with thyroglobulin. Lower S.I.'s were generally observed when human crude retinal extracts were used in the present study, and compared with those seen by Marak and associates[21] when crude ocular extracts were used as antigens in cultures with lymphocytes from patients with sympathetic ophthalmia.

The presence of both responders and nonresponders in the same clinical group suggests that possibly various clinical entities follow similar immune paths. Conversely, it appears that subgroups exist within clinical entities that are similar ophthalmoscopically.

The role of S-antigen in the pathogenic process is at this point speculative. A primary autoimmune role for the S-antigen can be invoked because patients are seen with severe ocular inflammation, S-antigen autosensitivity as determined by in vitro methods, and with no other causative factors being found. However, a secondary role may be played by the antigen in some patients. An initial process, such as toxoplasmosis, may be the inciting cause, with subsequent exposure of the normally sequestered S-antigen to the immune system and ultimate lymphocyte sensitization. In both cases, whether primary or secondary, the sensitization of the immune system to this highly antigenic material may help either perpetuate the disease or cause its recurrence. Additionally, variations in immune responsiveness may be the result of genetic predispositions, which may be reflected in HLA or B-cell alloantigen types. We may also assume that in order for autoimmunity to play a role in the immune response, various other factors such as possibly the correct immune environment would have to be present.

To the best of our knowledge, these results show for the first time, the presence of cellular immune memory to a purified retinal antigen in patients with ocular inflammatory disease. The present findings are corroborated by the initial data collected by Faure and associates (personal communication). Further definition of the role of S-antigen as well as other factors may help to elucidate mechanisms in ocular inflammatory disease.

Summary

S-antigen, an organ-specific substance isolated from the retinal photoreceptor region, was shown to be a potent agent for the induction of experimental autoimmune uveitis. S-antigen and other ocular antigens were tested for their ability to induce blast transformation of lymphocytes from patients with a variety of ocular inflammatory diseases. Lymphocytes from 22% of patients tested manifested a positive memory response to the S-antigen prepared from bovine eyes. Responses to human S-antigen paralleled those found with the bovine. All of those with a positive response had active or inactive retinal lesions. Some posterior uveitis patients responded to crude retinal extracts but not to S-antigen, indicating the possible role of other retinal antigens still to be purified. Control subjects did not manifest a positive immune response to the S-antigen, nor did patients with anterior uveitis. Possibly, these responses play some role in the pathogenesis of the disease.

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UVEITIS ASSOCIATED WITH SARCOIDOSIS AND ANGIOTENSIN CONVERTING ENZYME

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The simultaneous presence of granulomatous uveitis and systemic sarcoidosis usually leads to the diagnosis of sarcoid uveitis. However, patients with granulomatous uveitis may not have the typical clinicoradiographic findings of sarcoidosis or histologic evidence of noncaseating granulomas. Because there are no pathognomonic ophthalmologic findings of sarcoidosis, a biochemical marker for sarcoidosis would be a useful diagnostic adjuvant in these cases.

Increases of serum angiotensin converting enzyme have been associated with active sarcoidosis.[1,2] Although not specific for this disease, angiotensin converting enzyme may represent a sensitive biochemical marker for it when corroborating signs are present. In this study, the angiotensin converting enzyme activity of patients with granulomatous uveitis in the presence or absence of systemic sarcoidosis was evaluated.

SUBJECTS AND METHODS

Patients were divided into three groups as follows:

Group 1 (Systemic sarcoidosis)—Twenty patients with systemic sarcoidosis as determined by clinicoradiographic findings and positive biopsy findings. All of them had ophthalmic manifestations of sarcoidosis and ten had uveitis.

Group 2 (Granulomatous uveitis)—Twenty-seven patients with granulomatous uveitis (according to the criteria of Woods[3]) and no evidence of systemic sarcoidosis. Those patients with granulomatous uveitis in whom a uveitis syndrome was identified were excluded from this group and placed in Group 3. Complete blood cell counts, luetic serology, and serum calcium were within normal limits in all cases. Chest x-rays were either normal or showed nonspecific changes that were not typical of sarcoidosis. Nonreactive purified protein derivatives and positive cutaneous delayed hypersensitivity were present in all but three cases. Two of these three cases were not tested with universal skin antigens, however.

Group 3 (Other uveitis syndromes)—Seventeen patients with other uveitis syndromes, both granulomatous and nongranulomatous (four patients with toxoplasmosis; three with chronic cyclitis; two with Behçet's disease, ankylosing spondylitis, tuberculosis; and one with Fuchs' heterochromic cyclitis, acute multifocal placoid pigment epitheliopathy, histoplasmosis, and birdshot choroidopathy). Patients with uveitis who did not fit into well-recognized syndromes were excluded from this group. All patients were examined by us during the period from 1978 to 1979. Controls consisted of sera from 72 normal subjects who were not age- or sex-matched to any of the other groups.

After informed consent was obtained,

From the Clinical Research Center for Eye Disease of the Department of Ophthalmology (Dr. Weinreb), and the Francis I. Proctor Foundation for Research in Ophthalmology (Dr. Kimura), University of California School of Medicine, San Francisco, California. This study was supported in part by a Sammy Davis Jr. Award from Fight for Sight, Inc., New York City (Dr. Weinreb). Presented at the 115th Annual Meeting of the American Ophthalmological Society, Hot Springs, Virginia, May 29, 1979.

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peripheral venous blood was drawn and allowed to clot for approximately one hour at room temperature. The serum was removed and stored at −20°C. Angiotensin converting enzyme was assayed by using the method of Lieberman.[4] The serum sample was incubated with Hippuryl-Histidyl-Leucine; the hippuric acid liberated by the action of angiotensin converting enzyme on the substrate was extracted and quantitated spectrophotometrically. The mean serum angiotensin converting enzyme level in 72 normal subjects was 22± 6.3 (S.D.) nanomol/ml/min. Three of the 72 normal subjects (4.2%) had angiotensin converting enzyme activity exceeding two standard deviations above the mean. This is consistent with other studies.[5]

Results

Women outnumbered men in all groups (Table 1). In Group 1 (systemic sarcoidosis) 13 patients (65%) were black and in Group 2 (granulomatous uveitis), 17 patients (68%) were black. In Group 3 (other uveitis syndromes) ten (65%) patients were white.

The median age was lowest (33 years) and the number of patients who were using either topical or systemic corticosteroids at the time of angiotensin converting enzyme determination was highest (10, 37%) in Group 2. Only two (12%) patients in Group 3 were using corticosteroids, whereas seven (35%) were using them in Group 1.

Angiotensin converting enzyme activity for all groups and control subjects is depicted schematically in Figure 1. Because corticosteroid administration may lower angiotensin converting enzyme activity in certain individuals,[6] each group has been divided into two subgroups. The corticosteroid subgroup consists of those subjects who were using either topical or systemic corticosteroids at the time of angiotensin converting enzyme determination; subjects in the no corticosteroid subgroup were not using corticosteroids at that time. Angiotensin converting enzyme activity for both the control subjects and Group 3 was almost always within two standard deviations of the mean. In contrast, angiotensin converting enzyme values for many of the patients in Groups 1 and 2 exceeded the mean by two standard deviations or more. This was particularly noticeable for the patients who were not using corticosteroids.

TABLE 1

Clinical data

Groups*	No. of Patients	Age†	Sex		Race			No. Using Corticosteroids‡
			Male	Female	White	Black	Other	
Control patients	72	31	35	37	—	—	—	—
Systemic sarcoid	20	37	6	14	5	13	2	7
Granulomatous uveitis	27	33	6	21	8	17	2	10
Other uveitis syndromes	17	46	7	10	10	6	1	2

*Group 1 (systemic sarcoid); Group 2 (granulomatous uveitis); Group 3 (other uveitis syndromes).
†Median age for group in years.
‡Number of patients using either topical or systemic corticosteroids at the time of angiotensin converting enzyme determination.

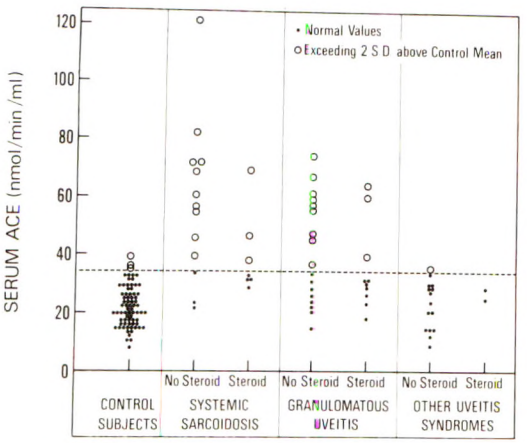

Fig. 1 (Weinreb and Kimura). Angiotensin converting enzyme activity in unveitis, systemic sarcoidosis, and controls.

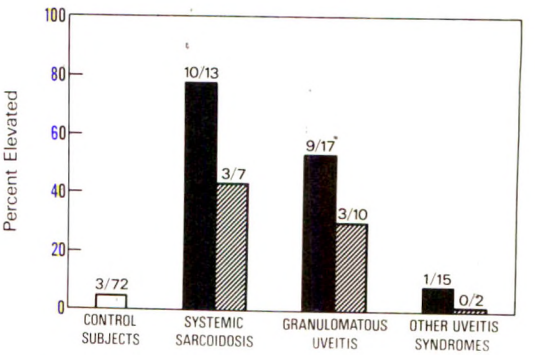

Fig. 2 (Weinreb and Kimura). Increased angiotensin converting enzyme activity in uveitis, systemic sarcoidosis, and controls. Fractions represent angiotensin converting enzyme values for each group exceeding two standard deviations above the mean. Group 1 (systemic sarcoidosis); Group 2 (granulomatous uveitis); Group 3 (other uveitis syndromes). Solid bars indicate no corticosteroids used; shaded bars indicate corticosteroids used.

Figure 2 shows the similar number of patients with increased angiotensin converting enzyme activity in Groups 1 and 2, and the small number of increased angiotensin converting enzyme values in the control subjects and Group 3. Compared to controls, mean angiotensin converting enzyme activity in Groups 1 and 2 was significantly increased (Table 2). In contrast, mean angiotensin converting enzyme activity for Group 3 was not significantly different when compared with controls.

TABLE 2

MEAN ANGIOTENSIN CONVERTING ENZYME ACTIVITY IN UVEITIS, SARCOIDOSIS, AND CONTROLS

Groups	Mean ± S.E.* and (P value)†	
	No Corticosteroid	Corticosteroid‡
Control subjects	22.0 ± 0.7	—
Systemic sarcoid	57.9 ± 7.4 (P < .001)	40.3 ± 5.1 (P < .02)
Granulomatous uveitis	41.5 ± 4.4 (P < .001)	35.6 ± 4.8 (P < .05)
Other uveitis syndromes	23.4 ± 2.1 (P > .2)	27.0 ± 2.0 (P > .5)

*nanomol/min/ml.

†Two-tailed P value compared with controls, using the two-independent sample *t*-test with separate variance estimates.

‡Patients using topical or systemic corticosteroids at the time of angiotensin converting enzyme determination.

DISCUSSION

The present study focused on the question of whether patients with granulomatous uveitis, who lacked clinicoradiographic and histologic evidence of sarcoidosis, had increased serum angiotensin converting enzyme activity.

In Group 2 compared with controls, a highly significant increase of mean angiotensin converting enzyme activity was found. Mean angiotensin converting enzyme activity was also increased in Group 1, as would be expected because the association of increased angiotensin converting enzyme values with active sarcoidosis is well described.[1,2] In contrast, no significant statistical difference was found for Group 3. Furthermore, the number of patients with angiotensin converting enzyme values exceeding two standard deviations above the control mean was similarly increased for Groups 1 and 2 when

compared with Group 3 and controls. These data clearly indicate that angiotensin converting enzyme activity was increased in some patients with granulomatous uveitis and no other evidence of sarcoidosis.

Because corticosteroids tend to diminish angiotensin converting enzyme activity in patients with sarcoidosis,[6] the effect of corticosteroids on angiotensin converting enzyme activity was also studied. Seven patients in Group 1 were using systemic corticosteroids (two, in combination with topical corticosteroids) for various durations at the time of angiotensin converting enzyme determination. These patients had significantly lower mean angiotensin converting enzyme activity than those in the no corticosteroid subgroup, thereby confirming other studies. In Group 2, ten patients were using topical corticosteroids (one, in combination with systemic corticosteroid) for various durations at the time of angiotensin converting enzyme determination. In this group, also, mean angiotensin converting enzyme activity of corticosteroid patients was lower than the no corticosteroid subgroup. For both Groups 1 and 2, the percentage of patients with increased angiotensin converting enzyme activity was lower in the corticosteroid subgroup. It appears that the increased angiotensin converting enzyme activity of Group 2 patients may be suppressed by even the topical administration of corticosteroids. In Group 3, only two patients were using corticosteroids and a valid comparison to the no corticosteroid subgroup could not be made.

Although it is not absolutely specific, in the absence of supporting clinical or histologic evidence, serum angiotensin converting enzyme appears to be of value as a biochemical marker for sarcoidosis. The number of false-positives is low; in this study it was 4.2% for healthy controls and 5.9% for other uveitis syndrome patients, which is similar to that found by others.[5] Also, increased angiotensin converting enzyme activity has been reported to occur only in leprosy,[7] Gaucher's disease,[8] and primary biliary cirrhosis,[9] in addition to sarcoidosis. The ophthalmologic pattern associated with these entities is easily distinguished from that found in sarcoidosis. A mild chronic iritis occurs in about one fifth of the patients with leprosy.[10] However, the presence of iris pearls (lepromas) and iris atrophy as well as the association with other ocular and systemic findings is rarely recognized. Gaucher's disease and primary biliary cirrhosis have not been associated with granulomatous uveitis and are also uncommon. Therefore, the simultaneous presence of granulomatous uveitis that does not fit into a well-recognized syndrome and increased serum angiotensin converting enzyme activity is strong evidence that the uveitis is associated with sarcoidosis (sarcoid uveitis).

The source of the increased serum angiotensin converting enzyme activity in these patients has not been identified. If systemic disease is absent, then perhaps sarcoid granulomas in the eye are producing enough angiotensin converting enzyme to result in increased serum levels. Because serum angiotensin converting enzyme levels probably reflect the total body mass of granulomas,[13] it is more reasonable that clinically quiescent sarcoidosis is present, which cannot be detected by current diagnostic means. Gallium scans may be useful in differentiating these two alternatives, because they can show uptake in certain small units of intensely involved tissues such as lacrimal glands and possibly the globe.

It has been reported that increased serum lysozyme levels might be useful in diagnosing sarcoidosis,[11] especially for patients with a clinical appearance of sarcoid uveitis.[12] Serum lysozyme is increased in a large number of conditions,

however, and therefore is of less value in diagnosis and management.

At least one fifth of patients with sarcoidosis develop symptoms related to the eye or its adnexa as the first signs of their disease.[14] Our results indicate that ocular involvement in sarcoidosis may be more common than generally recognized; additionally, it may be diagnosed in the absence of otherwise undetectable systemic disease. Because early recognition and treatment of ocular sarcoid may prevent visual loss, angiotensin converting enzyme may also be a useful ancillary diagnostic test for patients with iris nodules, acute iritis, conjunctival lesions, band keratopathy, chorioretinitis, periphlebitis, chorioretinal nodules, vitreous cells or hemorrhage, retinal or optic disk neovascularization, and lacrimal gland or optic nerve disease of unknown cause.

Serum angiotensin converting enzyme provides an inexpensive, rapid, and reliable screening test for systemic sarcoidosis, especially in the presence of corroborative signs. However, the definite diagnosis of sarcoidosis, either systemic or ocular, depends on histologic confirmation in the appropriate tissue. Because intraocular tissue is not easily obtainable, evaluation of serum angiotensin converting enzyme may prove to be a useful indicator of ocular sarcoid.

Summary

We evaluated serum angiotensin converting enzyme activity in three groups of patients as follows: 20 patients with systemic sarcoidosis and ophthalmic manifestations of the disease (Group 1); 27 patients with granulomatous uveitis and no evidence of systemic sarcoidosis (Group 2); and 17 patients with well-defined uveitis syndromes, both granulomatous and nongranulomatous (Group 3). Serum angiotensin converting enzyme activity in control subjects was 22.0 ± 0.7 nanomol/min/ml (mean ± S.E.). Compared to control subjects, serum angiotensin converting enzyme activity was significantly increased in Groups 1 and 2 for patients not using corticosteroids (57.9 ± 7.4 and 41.5 ± 4.4 nanomal/min/ml, respectively) as well as those using corticosteroids (40.3 ± 5.1 and 35.6 ± 4.8 nanomal/min/ml). Enzyme activity was not significantly different from controls for Group 3. Our study shows that the increase of serum angiotensin converting enzyme activity in some patients with granulomatous uveitis is strong evidence of sarcoid uveitis even in the absence of clinicoradiographic or histologic findings of systemic sarcoidosis.

Acknowledgment

Bio-Science Laboratories, Van Nuys, California, assayed the angiotensin converting enzyme.

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Ophthalmic miniature

No one knew for certain exactly when she began to lose vision. Even in later years, when she could no longer lift herself from the bed, it seemed that she was simply decrepit, and no one discovered that she was blind. . . .

She undertook a silent apprenticeship, learning distances of objects and people's voices in order to continue seeing with her memory those things denied her by the shadows of her cataracts.

Gabriel Garcia Marquez, *Cien Años de Soledad*
Barcelona, Plaza and Janes, SA: 1975

RETINAL ARTERIOVENOUS ANASTOMOSES IN THE VOGT-KOYANAGI-HARADA SYNDROME

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Congenital arteriovenous anastomoses have been frequently reported and are often associated with similar intracranial and extracranial vascular malformations.[1–4] Acquired retinal arteriovenous anastomoses occur in diseases in which retinal capillary nonperfusion is a feature, such as Takayasu's disease, diabetic retinopathy, and sickle-cell retinopathy.[5]

The Vogt-Koyanagi-Harada syndrome is characterized by diffuse bilateral intraocular inflammation and secondary exudative retinal detachments associated with alopecia, vitiligo, poliosis, and dysacousia.[6] Signs of central nervous system involvement include meningeal irritation, increased protein levels, and pleocytosis of the cerebrospinal fluid.

The patient described here had typical features of the Vogt-Koyanagi-Harada syndrome. Acquired retinal arteriovenous anastomoses developed in areas of altered pigment epithelium in both eyes and were documented by fundus photography and fluorescein angiography. To the best of our knowledge, this is the first reported case of an acquired arteriovenous anastomosis secondary to chronic uveitis.

CASE REPORT

A 15-year-old black girl was admitted to the Los Angeles County-University of Southern California Medical Center on Jan. 25, 1978, because of a six-week history of photophobia, redness, and tearing and a three-week history of decreased vision in both eyes. For ten days before admission, she had severe bilateral frontal and occipital headaches. Her medical history was unremarkable.

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Results of general physical examination and neurologic examination were normal. No changes in hair or skin were noted. Ocular examination disclosed a visual acuity of R.E.: 6/60 (20/200) and L.E.: hand motions. The anterior chamber showed a 2+ ciliary flush and 2+ cells and flare in each eye. The lens was normal in each eye. Applanation pressure was 10 mm Hg in both eyes. Ophthalmoscopic examination revealed bilateral bullous and inferior retinal detachments with macular involvement in the left eye.

Fluorescein angiography was performed on Jan. 30, 1978, and showed diffuse leakage of dye in both eyes from multiple pinpoint dots at the level of the retinal pigment epithelium that progressively accumulated in the subretinal space. Diffuse leakage of dye from both optic disks was also observed.

Lumbar puncture was performed and showed 285 lymphocytes and a normal protein level. Results of other laboratory tests, including chest x-ray film, complete blood cell count, serum chemistries, liver enzymes, blood serology, and urinalysis were normal. Intermediate strength tuberculin skin test was negative. An audiogram performed one week after admission was normal.

The patient was treated initially with topical corticosteroids, cycloplegics, periocular corticosteroid injections, and 100 mg of prednisone orally daily. The prednisone was increased to 150 mg daily when the detachments progressed in each eye. The retinal detachments resolved over a three-week period and visual acuity improved to R.E.: 4/60 (12/200) and L.E.: 2/60 (6/200).

Ophthalmoscopic examination of the right eye on Feb. 21, 1978, showed a "motheaten" appearance secondary to marked alteration of the pigment epithelium (Fig. 1, left). Several zones of dense subretinal hyperpigmentation radiated from the optic disk. Fluorescein angiography showed diffuse hyperfluorescence in areas of hypopigmentation and blockage of dye in areas of dense pigment deposition (Fig. 1, right).

On Jan. 3, 1979, approximately one year after the onset of symptoms, a one disk-diameter area of subretinal and intraretinal exudate was noted inferior to the right optic disk (Fig. 2, left). Fluorescein angiography, in the early anteriovenous phase of the right eye showed rapid flow of dye through a network of vessels representing an anteriovenous malformation (Fig. 2, right). The retinal artery feeding the shunt had increased in size. Focal capillary nonperfusion was present and the capillaries surrounding the shunt were dilated and leaked dye into the surrounding retina and subretinal space.

On Feb. 21, 1978, the left fundus showed similar extensive alteration of the pigment epithelium with

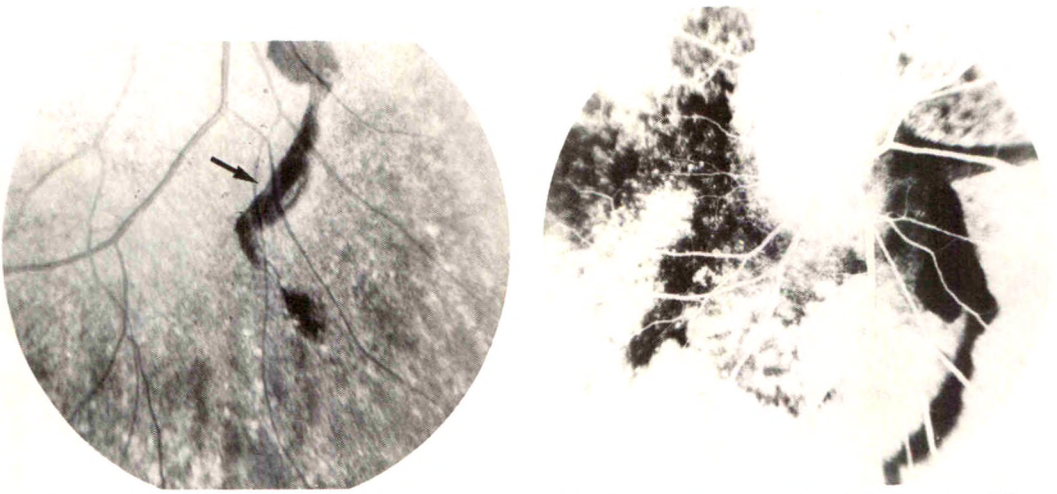

Fig. 1 (Manger and Ober). Left, Fundus photograph of right eye on Feb. 21, 1978, showing diffuse pigment epithelial atrophy and an irregular, linear zone of dense subretinal hyperpigmentation extending inferior to the optic disk. An arteriovenous anastomosis developed in this hyperpigmented zone (arrow) approximately ten months later. Right, Late fluorescein angiogram of right eye showing diffuse hyperfluorescence in areas of hypopigmentation and blockage of dye by dense hyperpigmentation surrounding the optic disk.

areas of hypopigmentation and scattered areas of dense hyperpigmentation (Fig. 3, left). Fluorescein angiography revealed complete blockage of dye by the dense accumulation of pigment and there were no apparent overlying retinal vascular changes (Fig. 3, right). On May 22, 1978, an arteriovenous anastomosis was noted in the area of pigment alteration superonasal to the optic disk (Fig. 4, top left). Extensive intraretinal and subretinal exudate surrounding the anastomosis was present, which elevated the retina. Fluorescein angiography showed a dilated feeder vessel emptying into several dilated

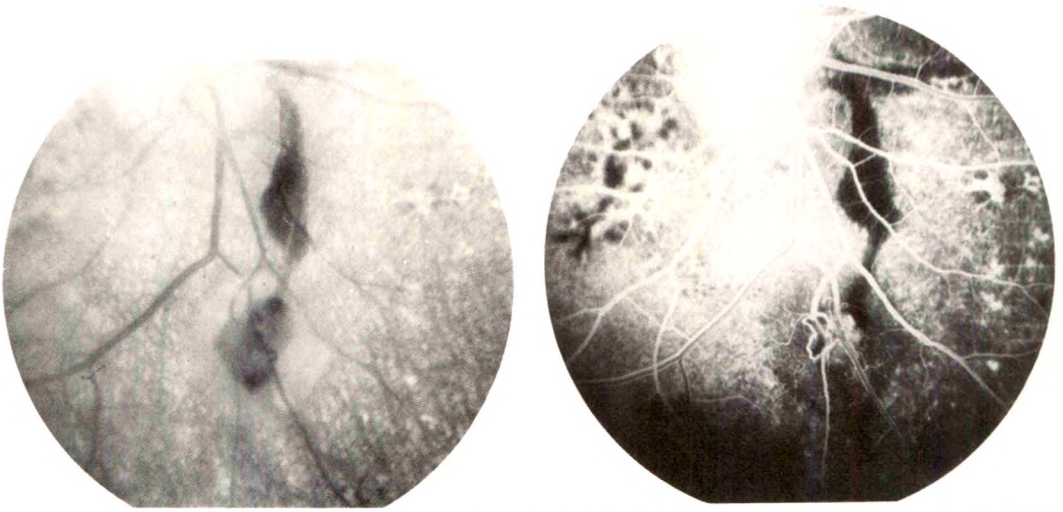

Fig. 2 (Manger and Ober). Left, Fundus photograph of right eye on Jan. 3, 1979, showing subretinal and intraretinal exudates surrounding vessels in zone of hyperpigmentation inferior to optic disk. Right, Fluorescein angiogram of right eye in early arteriovenous phase showing arteriovenous malformation inferior to the optic disk. Retinal artery feeding shunt has increased in size and dilated capillaries surrounding shunt leak dye. The lack of capillary detail in the area adjacent to the shunt represents capillary nonperfusion. Note complete filling of retinal vein just proximal to shunt whereas other retinal veins show laminar flow with partial filling. Dye is also seen leaking from the optic disk.

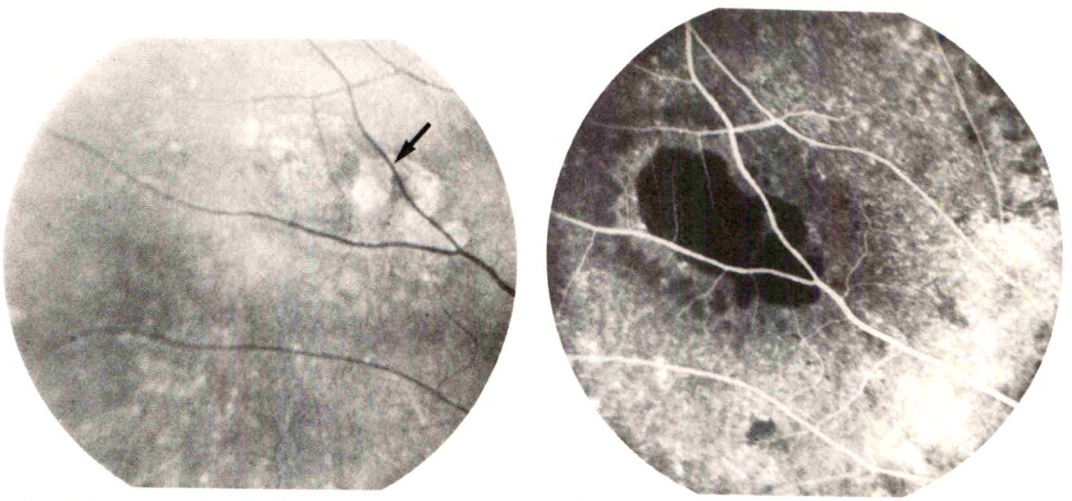

Fig. 3 (Manger and Ober). Left, Fundus photograph of left eye on Feb. 21, 1978, showing severe alteration of pigment epithelium superonasal to optic disk. An arteriovenous anastomosis developed in this area (arrow) approximately four months later. Right, Late fluorescein angiogram of left eye showing blockage of fluorescein by dense hyperpigmentation in area that later developed arteriovenous anastomosis. There are no apparent retinal vascular abnormalities.

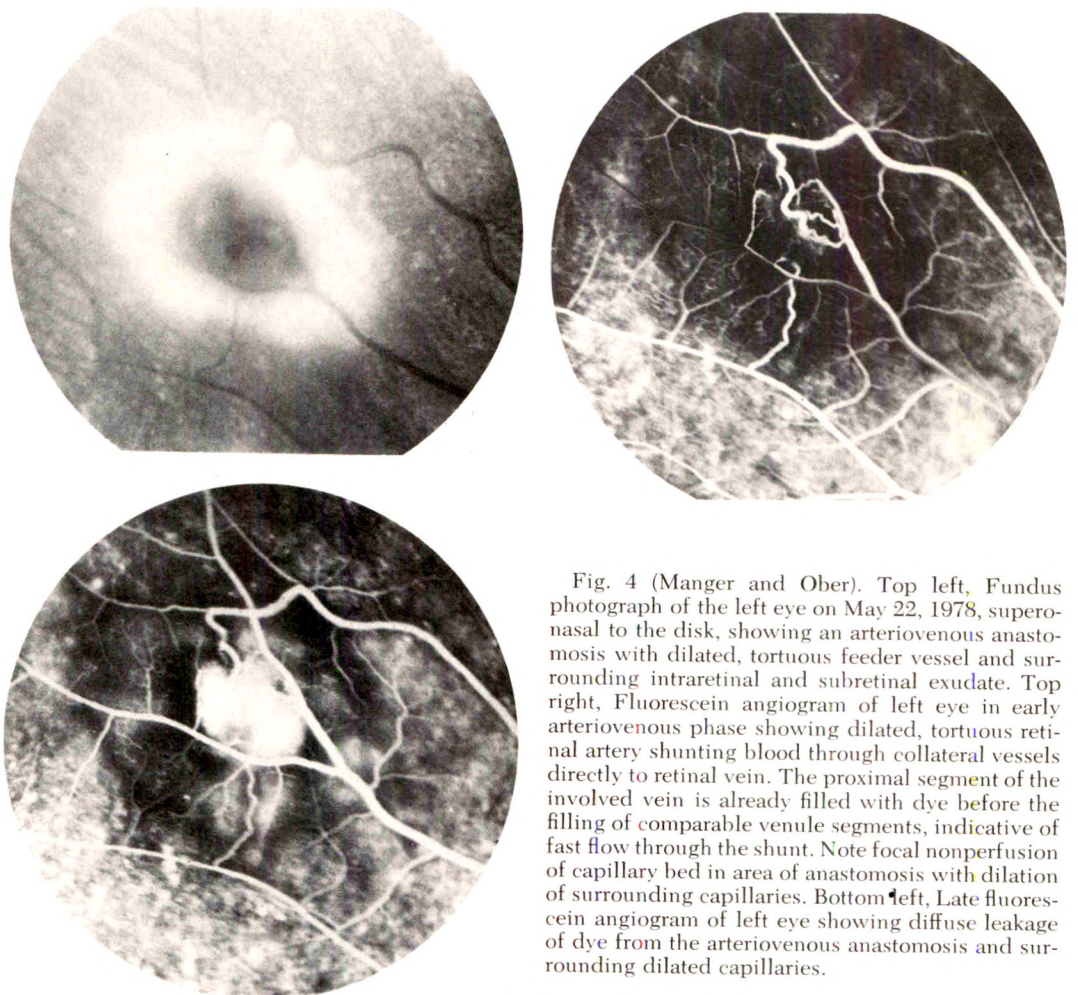

Fig. 4 (Manger and Ober). Top left, Fundus photograph of the left eye on May 22, 1978, superonasal to the disk, showing an arteriovenous anastomosis with dilated, tortuous feeder vessel and surrounding intraretinal and subretinal exudate. Top right, Fluorescein angiogram of left eye in early arteriovenous phase showing dilated, tortuous retinal artery shunting blood through collateral vessels directly to retinal vein. The proximal segment of the involved vein is already filled with dye before the filling of comparable venule segments, indicative of fast flow through the shunt. Note focal nonperfusion of capillary bed in area of anastomosis with dilation of surrounding capillaries. Bottom left, Late fluorescein angiogram of left eye showing diffuse leakage of dye from the arteriovenous anastomosis and surrounding dilated capillaries.

and tortuous collateral vessels that appeared to have their origin from pre-existing capillary channels (Fig. 4, top right). Blood flowed rapidly through the anastomosis, filling the vein just proximal to the shunt. Another collateral vessel from the artery directly inferior to this lesion directed blood toward this area without passage through an intervening capillary bed. Capillary nonperfusion was noted in the area of the anastomosis with the surrounding capillaries appearing dilated. The late angiogram showed leakage of dye from the collateral vessels and the surrounding dilated capillaries (Fig. 4, bottom left).

Systemic prednisone was tapered, and the patient is presently taking topical dexamethasone (Decadron) and cycloplegics to control anterior segment inflammation. She has developed mild bilateral peripheral anterior synechiae, but intraocular pressures have remained normal and her best corrected visual acuity on March 6, 1979, was R.E.: 6/9 (20/30) and L.E.: 6/15 (20/50).

Discussion

Pathologic anastomoses of the retinal vessels are not an infrequent finding, and can occur between the retinal vessels and between the retinal and choroidal vasculature. Retinal interarterial anastomoses are relatively rare and may occur after branch arterial occlusion.[5] Retinal venous anastomoses are more common and develop after vein obstruction.[5] Retinochoroidal vascular anastomoses occur most frequently after chorioretinitis, particularly toxoplasmosis,[7,8] but may occur in severe hypertension,[8] senile disciform macular degeneration,[9] or after perforating trauma[10] or argon laser photocoagulation.[11] Retinal arteriovenous anastomoses may be congenital and are seen in the Wyburn-Mason syndrome and von Hippel's disease.[1–4] Acquired retinal arteriovenous anastomoses develop as a result of obliteration of the retinal capillary bed and occur in sickle cell hemoglobinopathies,[5] diabetic retinopathy,[5] Takayasu's disease,[5] and retrolental fibroplasia.[5,12]

The posterior segment findings in Vogt-Koyanagi-Harada syndrome include vitritis, papillitis, and acute choroiditis with secondary exudative, retinal detachments. The angiographic findings in the Vogt-Koyanagi-Harada syndrome have been described by Kanter and Goldberg.[13] They found multiple fluorescent dots at the level of the pigment epithelium that enlarged with time and leaked dye into the subretinal space. Diffuse pigment migration within the choroid and pigment epithelium was seen after the resolution of the inflammatory process. In our case there was no apparent involvement of the retinal vessels.

Although acute choroiditis is the distinguishing sign of the Vogt-Koyanagi-Harada syndrome, a few investigators have noted retinal and choroidal vascular abnormalities[13–15] (unpublished data). Epipapillary and peripapillary neovascularization has been reported in one case.[13] Perry and Font[14] found intraretinal hemorrhages with degenerative changes in the nerve fiber and ganglion cell layers in pathologic specimens. A hemorrhagic detachment of the macula has been reported in one case with the Vogt-Koyanagi-Harada syndrome.[15] Presumably, the underlying cause of the detachment was the development of subretinal neovascularization beneath the macula with hemorrhage beneath the neurosensory retina. Retinochoroidal anastomoses in areas of subretinal neovascularization have been observed in two patients with the Vogt-Koyanagi-Harada syndrome (R. R. Ober, Personal communication, 1978).

Henkind and Wise[5] described three types of retinal collateral vessels: arterioarteriolar, venovenular, and arteriovenous. They speculated that arteriovenous collateral vessels developed from existing capillaries in areas of capillary bed obstruction and reasoned that the collateral vessels resulted from increased flow and increased intravascular pressure within the capillary network. Blood flow through collateral vessels is usually slow and after they become well developed, leakage does not usually occur. Henkind and Wise[5] further described retinal vascular shunts as arteriovenous anastomoses, congenital or developmental, in which blood flowed directly, and usually rapid-

ly, from artery to vein without going through a normal capillary bed. No leakage is seen in the racemose angioma, however, shunts seen in retinal angiomatosis (von Hippel's disease) often show marked exudative and hemorrhagic lesions.

Our patient developed bilateral acquired retinal arteriovenous anastomoses approximately one year after the onset of symptoms in the right eye and five months after the onset of symptoms in the left eye. Vision was not affected by these lesions because of their extramacular location. Angiographic studies showed fast blood flow through both of the anastomoses, which is unusual for arteriovenous collateral vessels and more indicative of a shunt. Both lesions showed ophthalmoscopic and angiographic evidence of marked leakage of exudate into and beneath the surrounding retina, which is also unusual for arteriovenous collateral vessels. The angiographic studies of the left eye, however, showed dilated tortuous vessels developing from apparently normal pre-existing capillaries, confirming that these vessels are indeed collateral vessels and not shunts.

Retinochoroidal anastomosis in the Vogt-Koyanagi-Harada syndrome and other types of uveitis may be related to the destruction of Bruch's membrane and choriocapillaris allowing communication between the choroidal and retinal vasculature[7,8] (unpublished data). However, we find it more difficult to explain the occurrence of the retinal arteriovenous anastomoses seen in this case, because the retinal vasculature is not primarily involved in the Vogt-Koyanagi-Harada syndrome. The common denominator in all conditions featuring arteriovenous collateral vessels is nonperfusion of the retinal capillary bed with resulting ischemia of the retina. Development of collateral vessels may be an attempt to restore normal flow in the retinal vascular bed. The stimulus for the process, which is probably the same as that responsible for neovascularization in these conditions, is unknown. In our case intense inflammation of the underlying pigment epithelium and choroid may have caused focal damage and resultant closure of the retinal capillaries, which in turn, may have induced sufficient ischemia for the development of collateral vessels. These anastomoses occurred in areas of extensive pigment damage, and in both eyes there was angiographic evidence of capillary closure in the immediate area. However, we cannot document that the capillary closure preceded the development of the collateral vessels, and therefore this hypothesis remains speculative.

Summary

A 15-year-old black girl had acute bilateral uveitis and other features of the Vogt-Koyanagi-Harada syndrome. Several months after the onset of her illness, she developed acquired retinal arteriovenous anastomoses in both eyes. By using fluorescein angiography, we documented that the anastomoses were collateral vessels developing in areas of damaged retinal pigment epithelium and retinal capillaries.

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PERIPAPILLARY NEOVASCULAR MEMBRANES IN PRESUMED OCULAR HISTOPLASMOSIS

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Loss of central vision in presumed ocular histoplasmosis is usually the result of hypertrophic and atrophic macular scarring secondary to leakage from choroidal neovascularization entering the subretinal space through defects in Bruch's membrane. Neovascular ingrowth may also occur from peripapillary areas with resultant serous and hemorrhagic detachment of the retina, leading to permanent central scarring and visual loss when the fovea is involved.[1,2] Although the natural history[3–7] and photocoagulation treatment[6,8–14] of macular subretinal membranes have been well described, less is known about the management of peripapillary membranes.[2,15] We report herein our results in the management of 39 eyes with symptomatic peripapillary membranes associated with ocular histoplasmosis.

SUBJECTS AND METHODS

The records of all patients with peripapillary membranes secondary to ocular histoplasmosis referred to Retina Consultants, Ltd., in St. Louis, Missouri, since 1975 were reviewed. The diagnosis of ocular histoplasmosis was based on the presence of peripheral atrophic scars or typical peripapillary changes in either the involved or the fellow eye. Histoplasmosis skin testing was not routinely done. All patients had peripapillary membranes documented by intravenous fluorescein angiography. All patients were followed up for a minimum of six months. At each follow-up visit the symptoms, visual acuity, extent of serous detachment, and presence of hemorrhage or exudate were noted. Stereoscopic fundus photographs were taken at most visits. Repeat fluorescein angiography was performed as indicated. The distance of the leading edge of the neovascular membrane from the center of the avascular zone was measured with a scale using the early phase angiogram.

The decision to treat with photocoagulation was based on the clinical findings in individual cases. No attempt was made to randomize treatment or to match treated and untreated cases. All treatment was performed with the Zeiss xenon photocoagulator with the patient under retrobulbar anesthesia. The 3-degree spot size was used with intensities sufficient to whiten the inner retinal layers. Treatment included the entire area of neovascularization and extended 125 μ into normal retina where possible. Where the margins of the neovascularization were obscured by blood or cloudy exudate, the treatment was extended to include the area of blocked fluorescence (hemorrhage) where possible. Care was taken to reduce the intensity of treatment over hemorrhage or pigmented scars to avoid damage to the inner retinal layers. A fundus photograph was taken within 24 hours to evaluate the adequacy of treatment. Follow-up angiography was scheduled for two to four weeks after treatment to document total elimination of the membrane.

RESULTS

Thirty-nine eyes of 34 patients made up the study group. All patients were white;

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TABLE 1

CLINICAL FINDINGS IN THE INVOLVED EYE

	Untreated		Treated		Total	
	No.	%	No.	%	No.	%
Hemorrhage	15	75	17	89	32	82
Serous detachment of the fovea	9	45	15	79	24	62
Intraretinal exudates	3	15	9	47	12	31
Hemorrhagic detachment of the fovea	4	20	7	37	11	28
Inactive peripapillary scar with new focal activity	8	40	2	11	10	26

21 were women and 13 were men. The mean age was 39 years, with a range of 19 to 63 years. The average follow-up was 12 months, with a range of six to 38 months.

Clinical findings—The most frequent complaint was blurred vision. Other patients noted a scotoma or visual distortion. Some patients gave a history of intermittent symptoms in the involved eye for months or years. Serous detachment of the sensory retina was clinically present in all cases. Various amounts of subretinal hemorrhage and intraretinal exudate were noted (Table 1). Serous or hemorrhagic detachment of the fovea was twice as common in the patients selected for treatment. Activation from the edge of an inactive scar which represented a zone of previous neovascular activity was noted in ten cases (26%). In these cases the active zone was separated from the disk by a broad zone of subretinal scarring and marked pigment disruption (Fig. 1).

The fellow eye—Five patients (15%) had active peripapillary neovascular membranes in both eyes (Table 2). Evidence of extensive peripapillary scarring was noted in 15 fellow eyes (44%). In these cases subretinal fibrosis and marked pigment epithelial changes greater than one

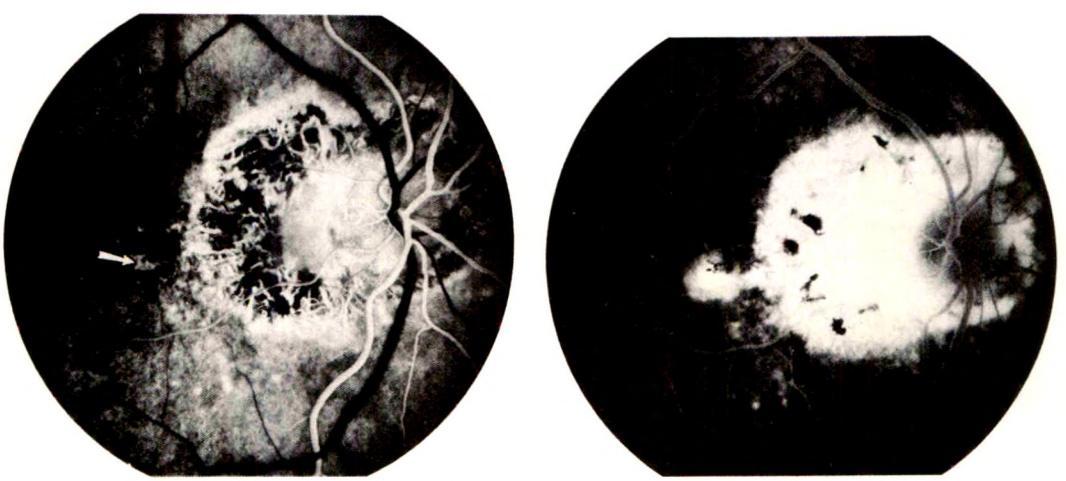

Fig. 1 (Cantrill and Burgess). Left, Early phase angiogram indicating neovascularization extending into the avascular zone (arrow) on the border of a large inactive peripapillary scar. Visual acuity: 6/60 (20/200). Right, Late phase angiogram demonstrating leakage from neovascular network and subretinal fibrous scar.

TABLE 2

CLINICAL FINDINGS IN THE FELLOW EYE

	No.	%
Active membrane	5	15
Inactive membrane	15	44
Visual acuity less than 6/60 (20/200)	10	29
Peripapillary atrophy	13	38
Peripheral scars	29	85

disk diameter in size were present, and we thought that these indicated previous neovascular activity. Ten of these patients (29%) had visual acuity of 6/60 (20/200) or less as a result of macular scarring secondary to previously active peripapillary disease. Typical small atrophic peripapillary changes were noted in 13 additional cases (38%). Peripheral atrophic scars were present in 29 eyes (85%). Only one fellow eye (3%) was free of peripheral or peripapillary changes.

Selection of cases for treatment—We selected 19 eyes for treatment on the basis of objective and subjective clinical findings. Six were treated because visual acuity was 6/60 (20/200) or less from prolonged serous or hemorrhagic macular detachment. Five were treated because the leading edge of the membrane was less than 1/2 disk diameter from the fovea. One patient was treated for documented increased growth of the subretinal membrane with progressive visual loss. We treated one patient who had cystoid macular edema. Seven eyes were treated in part because central vision had been lost in the fellow eye from peripapillary disease.

Twenty eyes were not treated. Six of these were considered clinically untreatable because of extension of the membrane beneath the fovea. Most of the remaining 14 eyes were electively followed up because the leading edge of the membrane was greater than one disk diameter from the fovea and central vision was not markedly decreased by serous or hemorrhagic detachment. Some of these eyes did have membranes less than 1/2 disk diameter from the fovea (three), visual acuity of 6/60 (20/200) or less from macular detachment (three), or documented growth of the membrane (three).

Visual results in untreated eyes—The average follow-up in the untreated eyes was 13 months. Six of the 20 untreated eyes (30%) were believed to be clinically untreatable because of extension of the peripapillary membrane beneath the fovea. None of these eyes had final visual acuity better than 6/60 (20/200) (Table 3). Central vision was lost in one patient with an enlarging membrane directly in the papillomacular bundle, which was not treated for fear of damaging the nerve fiber layer. The remaining 13 untreated eyes (65%) were electively followed up and all had final visual acuity of 6/12 (20/40) or better. The mean distance from the leading edge of the membrane to the center of the avascular zone in the eyes electively followed up was 1 1/4 disk diam-

TABLE 3

VISUAL RESULTS IN UNTREATED EYES

Distance from Fovea	No.	%	6/6-6/12 (20/20-20/40)	6/12-6/30 (20/40-20/100)	6/60 (20/200)
Less than 1/4 disk	6	30	0	0	6
1/4 to 1 disk	4	20	4	0	0
Greater than 1 disk	10	50	9	0	1
Total	20	100	13(65%)	. . .	7(35%)

eter. There was a significant correlation between visual outcome and proximity of the membrane to the fovea ($P<.001$), although the distribution of distances was skewed (Table 3). There was a less striking correlation of the final visual acuity with the initial visual acuity ($P<.01, \chi^2$ test). Correlation of hemorrhage in the central zone with final visual acuity was not significant, but the number of cases was small. Figure 2 illustrates a typical case electively followed up, with a good visual result.

Visual results in treated eyes—The average follow-up from the date of treatment in the treated group was 11 months. Twelve (63%) had a final visual acuity of 6/12 (20/40) or better (Table 4). The mean distance from the leading edge of the membrane to the fovea was 3/4 disk diameter. All three cases with membranes in which the leading edge was less than 1/4 disk diameter from the fovea lost central vision. The four eyes with membranes more than one disk diameter from the fovea had a final visual acuity of 6/12 (20/40) or better. Of the remaining 12 eyes, eight had excellent results; only two lost central vision. Again the final visual acuity was significantly correlated with the distance of the membrane from the fovea ($P<.01$). Initial visual acuity, how-

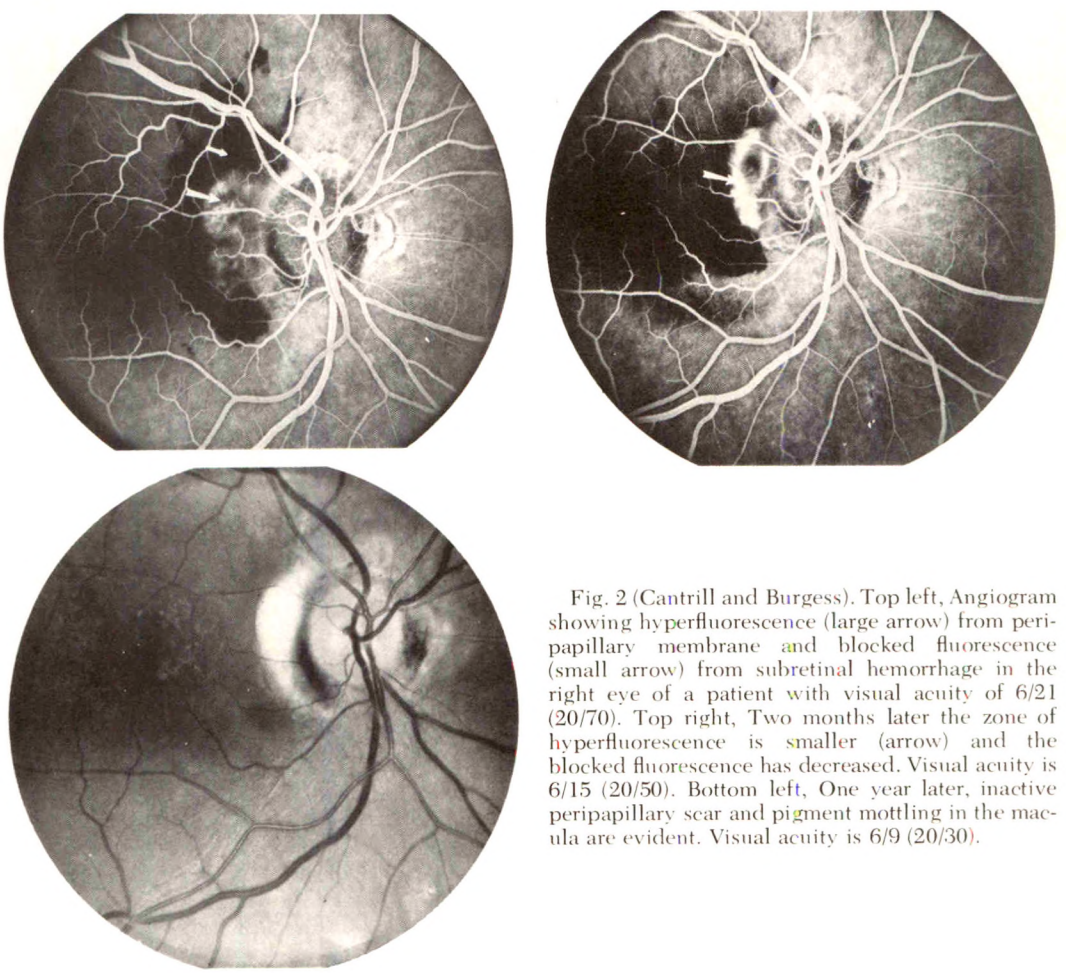

Fig. 2 (Cantrill and Burgess). Top left, Angiogram showing hyperfluorescence (large arrow) from peripapillary membrane and blocked fluorescence (small arrow) from subretinal hemorrhage in the right eye of a patient with visual acuity of 6/21 (20/70). Top right, Two months later the zone of hyperfluorescence is smaller (arrow) and the blocked fluorescence has decreased. Visual acuity is 6/15 (20/50). Bottom left, One year later, inactive peripapillary scar and pigment mottling in the macula are evident. Visual acuity is 6/9 (20/30).

TABLE 4

VISUAL RESULTS IN TREATED EYES

Distance from Fovea	No.	%	6/6-6/12 (20/20-20/40)	6/12-6/30 (20/40-20/100)	6/60 (20/200)
Less than 1/4 disk	3	16	0	0	3
1/4 to 1 disk	12	63	8	2	2
Greater than 1 disk	4	21	4	0	0
Total	19	100	12(63%)	2(11%)	5(26%)

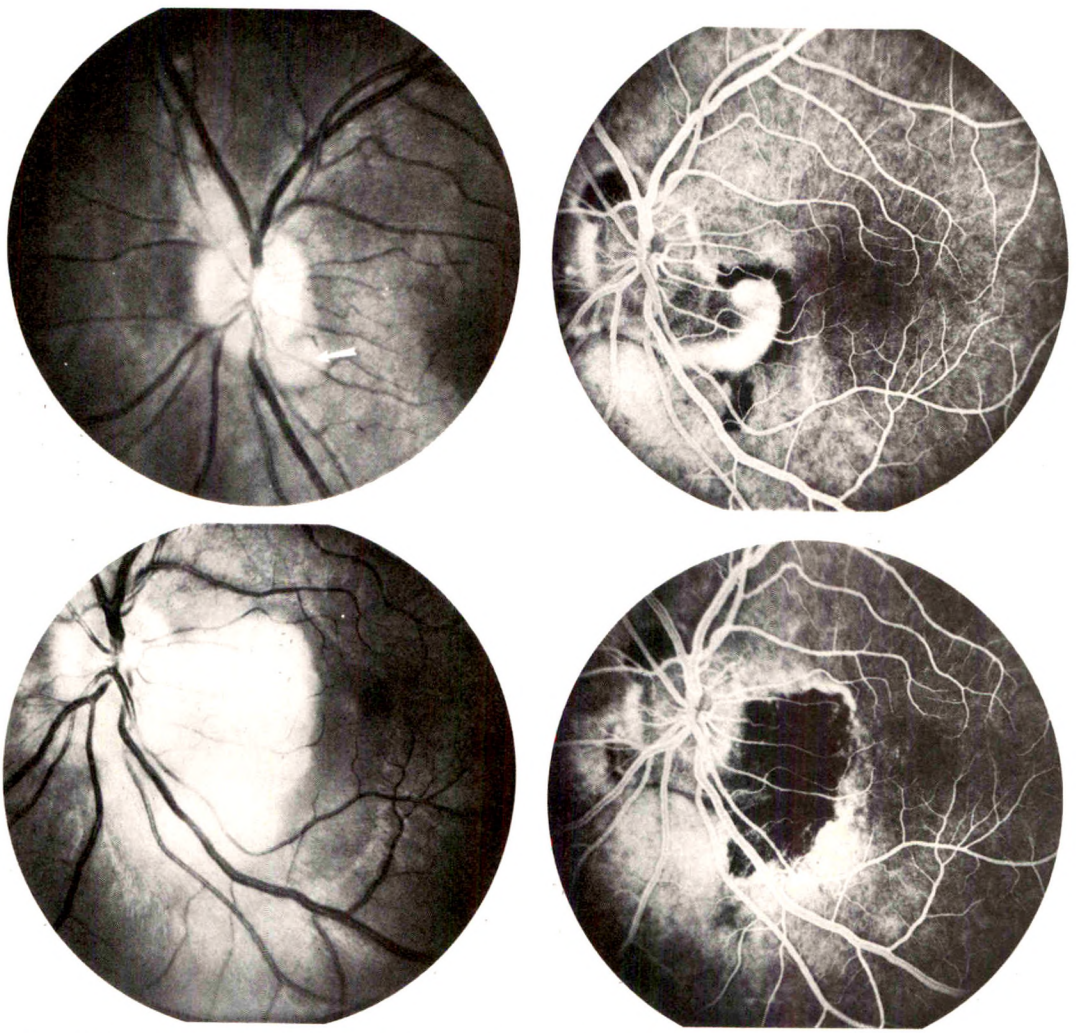

Fig. 3 (Cantrill and Burgess). Top left, A small zone of peripapillary atrophy (arrow), is present in an asymptomatic eye with visual acuity of 6/6 (20/20). Top right, Two years later the angiogram demonstrates hyperfluorescence from a neovascular membrane in the area of the previous peripapillary scar. Visual acuity is still 6/6 (20/20) with metamorphopsia. Bottom left, Red-free treatment photograph demonstrating coverage of the entire zone of neovascularization by photocoagulation. Bottom right, Two months later follow-up angiogram demonstrates no residual neovascularization and staining at the border of the photocoagulation scar. Visual acuity is still 6/6 (20/20).

ever, did not correlate with the final result (P>.1). Vision improved in nine, was unchanged in four, and worsened in six. Both the presence of serous detachment in the fovea and hemorrhage in the avascular zone were significantly correlated with a poorer visual result. Figure 3 demonstrates an adequately treated case with a good result.

Residual and recurrent membranes—The most common finding in unsuccessfully treated eyes was failure to eliminate the membrane completely. In seven eyes (37%), the follow-up angiogram demonstrated residual neovascularization. In four of these, the neovascularization was adequately surrounded by treatment and disappeared on follow-up angiography. One patient was inadequately treated, was retreated, and had a good result. Two eyes demonstrated residual neovascularization beyond the treatment margin extending into the avascular zone and they were untreatable at the time of repeat fluorescein angiography.

Four patients (21%) had frank recurrence of neovascularization six months or more after treatment. In all cases the treatment photograph demonstrated adequate coverage of the neovascularization, and the follow-up angiogram showed total elimination of all areas of hyperfluorescence (Fig. 4). One patient who was retreated, had a good visual result. Another recurred twice and was retreated twice with a poor visual result. The third patient was untreatable because of growth of the membrane into the avascular zone. In the fourth patient, membrane growth recurred on the nasal side of the disk and was followed up electively.

Evidence of recurrent neovascularization was also noted in the untreated group. Eight eyes (40%) demonstrated focal activity from the edge of a large peripapillary scar (Fig. 2). Four of these had histories of previous episodes of activity in the involved eye, which had spontaneously resolved. The prognosis was worse in these eyes because the leading edge of the neovascular membrane tended to be closer to the fovea. Five patients were clinically untreatable. There was a high incidence of bilateral disease in this group: seven fellow eyes showed extensive peripapillary scarring and four lost central vision as a result.

Treatment complicatons—Immediate increase in the amount of serous detachment following treatment occurred in five eyes (26%). Appearance of additional exudate was seen in four eyes (21%). Hemorrhage extending into the avascular zone immediately after treatment was noted in three eyes (16%). Although these factors may have delayed recovery after treatment, the final visual result was not significantly different from the results of other treated cases. Marked pigment mottling in the avascular zone resulted in seven eyes (37%), with visual results worse than 6/12 (20/40) in four eyes. Proximity of the membrane, requiring treatment close to the avascular zone, may have been the cause of a poor result in only one of these four eyes. Two had hemorrhage inside the avascular zone before treatment. One eye required treatment three times to eliminate all neovascularization. In these four eyes, depigmentation in the avascular zone may be related to damage to central photoreceptors from prolonged serous detachment, hemorrhage, or heat. Conversely, central pigment mottling was noted in five untreated eyes (25%), all with good visual results.

Heavy photocoagulation treatment within the papillomacular bundle may damage the nerve fiber layer with resultant visual loss. Pre- and postoperative visual fields were not routinely done, but the few cases in which they were done demonstrated only enlargement of the blind spot without arcuate defects. All treated cases had extensive serous detach-

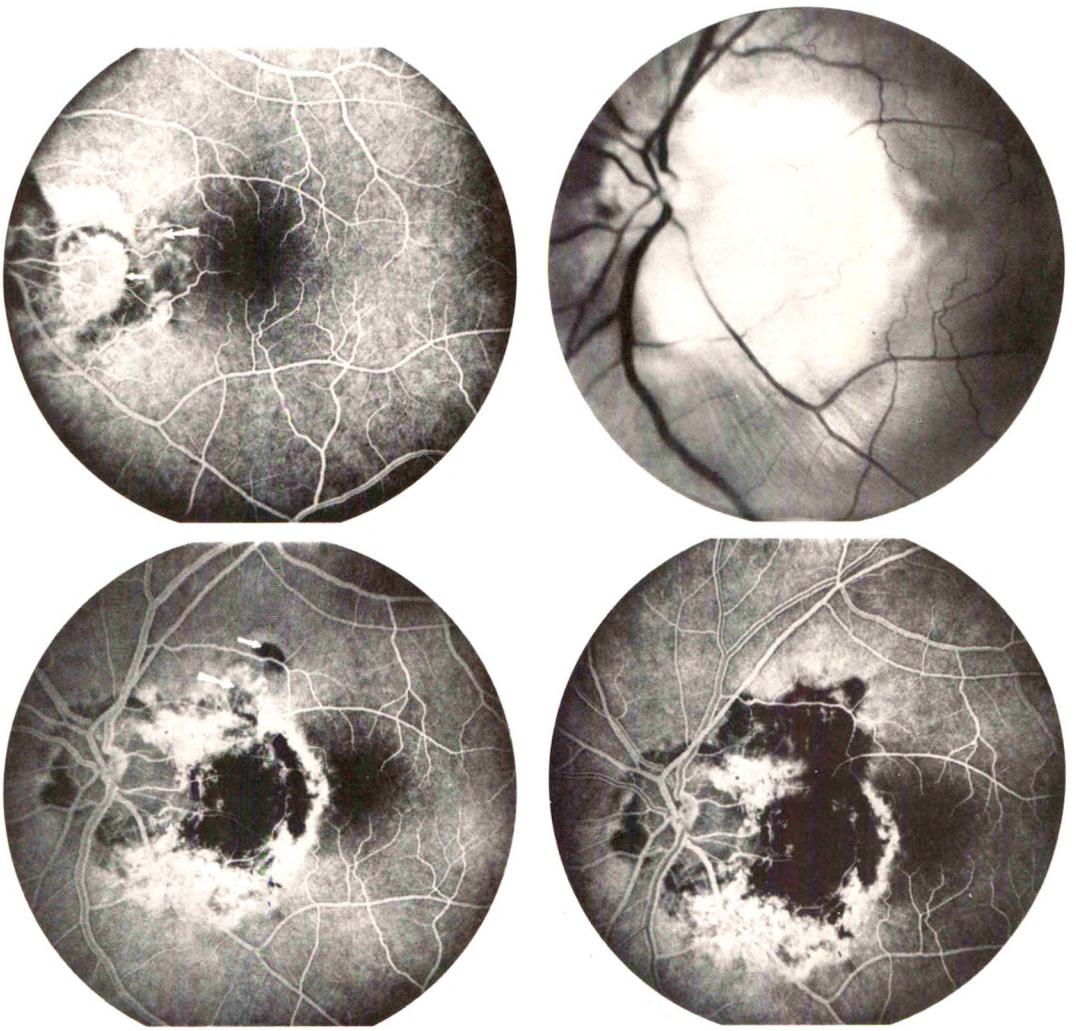

Fig. 4 (Cantrill and Burgess). Top left, Angiogram demonstrating neovascularization temporal to the disk margin (small arrow). There is a surrounding zone of pigment epithelial atrophy (large arrow). Visual acuity is 6/6 (20/20). Top right, Red-free treatment photograph demonstrates coverage of the entire membrane and surrounding pigment defects. Bottom left, One year later the angiogram demonstrates a zone of activity (large arrow) and hemorrhage (small arrow) at the superior margin of the photocoagulation scar. Bottom right, The angiogram after retreatment demonstrates elimination of the membrane. Visual acuity is 6/6 (20/20).

ment of the sensory retina, thus protecting the nerve fiber layer, so that good visual results despite heavy photocoagulation treatment are not surprising.

Discussion

The characteristic changes around the disk in ocular histoplasmosis were first described by Schlaegel and Kenney.[1] They separated peripapillary changes into asymptomatic nodular, diffuse and mixed types, and symptomatic hemorrhagic circumpapillary involvement. Nodular changes resemble the peripheral atrophic scars seen in patients with ocular histoplasmosis (Fig. 3, top left). The diffuse pattern is characterized by a zone of pigment epithelial atrophy outside a pig-

ment line usually on the temporal disk margin. These changes are seen in 18 to 28% of patients with ocular histoplasmosis,[16,17] and are considerably more common in patients with macular involvement.[5,6] The asymptomatic changes are presumably the result of disseminated choroiditis. Hemorrhagic circumpapillary involvement was not clearly distinguished from the other types, but is now known to be the result of neovascularization that enters the subretinal space through defects in Bruch's membrane in areas of peripapillary scarring. Loss of vision is caused by serous and hemorrhagic detachment of the sensory retina as a result of leakage from subretinal neovascularization.

In patients with ocular histoplasmosis, peripapillary neovascularization is less common than perimacular involvement. In their study of disciform macular detachments, Gass and Wilkinson[6] found only eight of 81 (10%) to be the result of peripapillary membranes. In their long-term follow-up of patients with ocular histoplasmosis, Schlaegel and Weber[4] reported 19 of 155 (12%) with peripapillary involvement. The risk of activation from atrophic peripapillary scars has also been found to be less. Only 4 to 6% of inactive peripapillary scars, as compared to 20 to 24% of inactive macular scars, develop serous or hemorrhagic sensory detachments over a two- to three-year follow-up period.[6,18] We found only one case that activated from a known inactive peripapillary scar in the fellow eye (Fig. 3).

The bilaterality of peripapillary disease was orginally noted by Schlaegel and Kenney,[1] although the prevalence of bilateral hemorrhagic disease was not discussed. In a small series of patients, Meredith and Aaberg[2] noted evidence of bilateral hemorrhagic activity in three of five patients. Five of our patients (15%) had bilateral active peripapillary membranes. We found extensive peripapillary scarring indicative of inactive neovascularization in 15 (44%) and loss of central vision in ten (29%) of the fellow eyes. Furthermore, four of our patients (10%) now have bilateral loss of central vision caused by peripapillary disease. Similar results have been reported for macular disease with 30 to 44% showing bilateral disease and 27 to 32% losing central vision in the fellow eye.[3,6] Involvement of the fellow eye in our cases took the form of peripapillary disease rather than macular disease most of the time. Two additional patients lost vision in the fellow eye from macular subretinal neovascularization.

The course of untreated peripapillary neovascular membranes in patients with ocular histoplasmosis is not well known. Schlaegel and Weber[4] found seven eyes (37%) with visual acuity of 6/9 (20/30) or better and nine eyes (47%) with visual acuity of 6/60 (20/200) or less in 19 patients followed up at least four years. These visual results are not significantly different from the course of macular disease with preservation of reading vision in 23 to 30% and loss of central vision in 45 to 57%.[4,5] Other uncontrolled studies of untreated macular subretinal membranes in patients with ocular histoplasmosis stress a strong correlation between final visual acuity and distance of the leading edge of the membrane from the center of the fovea (Table 5).[3,6,7,13] Our untreated cases cannot be compared to these results since they were not randomized or matched to treated cases and were clinically selected for their good (or bad) prognosis.

There is no large series that gives the results of photocoagulation in the management of peripapillary membranes in patients with ocular histoplasmosis. Case reports by Meredith and Aaberg[2] and Jack[15] indicate that good results can be obtained. The results of photocoagulation of macular subretinal membranes are variable in uncontrolled series, which report

TABLE 5

RELATIONSHIP OF VISUAL RESULTS TO PROXIMITY OF THE NEOVASCULAR MEMBRANE TO THE FOVEA IN UNTREATED PATIENTS*

Study	Membranes < 1/4 DD		Membranes ≥ 1/4 DD	
	No. of Patients	6/12 VA≥ (20/40)	No. of Patients	6/12 VA≥ (20/40)
Okun[13]†	18	4 (22%)	4	4 (80%)
Gass and Wilkinson[6]	27	6 (22%)	11	7 (64%)
Elliot and Jackson[7]	16	2 (12%)	19	7 (37%)
Klien and associates[3]	36	9 (25%)	28	18 (64%)
Present study	6	0	14	13 (93%)

*DD designates disk diameter; VA, visual acuity.
†Final visual acuity of 6/9 (20/30) or better.

19 to 71% of cases retaining visual acuity of 6/12 (20/40) or better.[6,8,9,12,13] These results can also be explained by the relationship of visual prognosis to the distance of the membrane from the fovea (Table 6). Those studies in which the greatest percentage of patients had proximal membranes had the worst visual results.

Our results suggest that peripapillary neovascular membranes, treated or untreated, generally have a better prognosis than macular membranes, partly because they usually do not extend to within 1/4 disk diameter of the center of the fovea. Conversely, when a peripapillary membrane does extend to within 1/4 disk diameter of the fovea the prognosis is poor. All of our patients, treated or untreated, lost central vision in this situation, although other investigators report some success in macular cases, both treated and untreated.[3,6–8,12,13] Other factors such as initial visual acuity, serous detachment of the fovea, and hemorrhage in the avascular zone tended to correlate with poor results in our study, but these factors are directly related to the size and proximity of the membrane to the fovea.

Gass and Wilkinson[6] stressed the need to treat macular neovascular membranes heavily. Ten of their 13 patients with photocoagulation failure were treated inadequately, as determined by the intensi-

TABLE 6

RELATIONSHIP OF VISUAL RESULTS TO PROXIMITY OF THE NEOVASCULAR MEMBRANE TO THE FOVEA IN TREATED PATIENTS*

Study	Membranes < 1/4 DD		Membranes≥ 1/4 DD	
	No. of Patients	6/12 VA≥ (20/40)	No. of Patients	6/12 VA≥ (20/40)
Okun[13]†	53	8 (15%)	10	4 (40%)
Gass and Wilkinson[6]	15	3 (20%)	15	9 (60%)
Gitter and Cohen[9]	2	0%	16	10 (62%)
Elliot and Jackson[14]	—	—	30	12 (40%)
Klein, Fine, and Patz[8]	6	3 (50%)	25	19 (76%)
Sabates, Lee, and Sabates[12]	42	11 (26%)	22	15 (68%)
Present study	3	0	16	12 (75%)

*DD designates disk diameter; VA, visual acuity.
†Final visual acuity of 6/9 (20/30) or better.

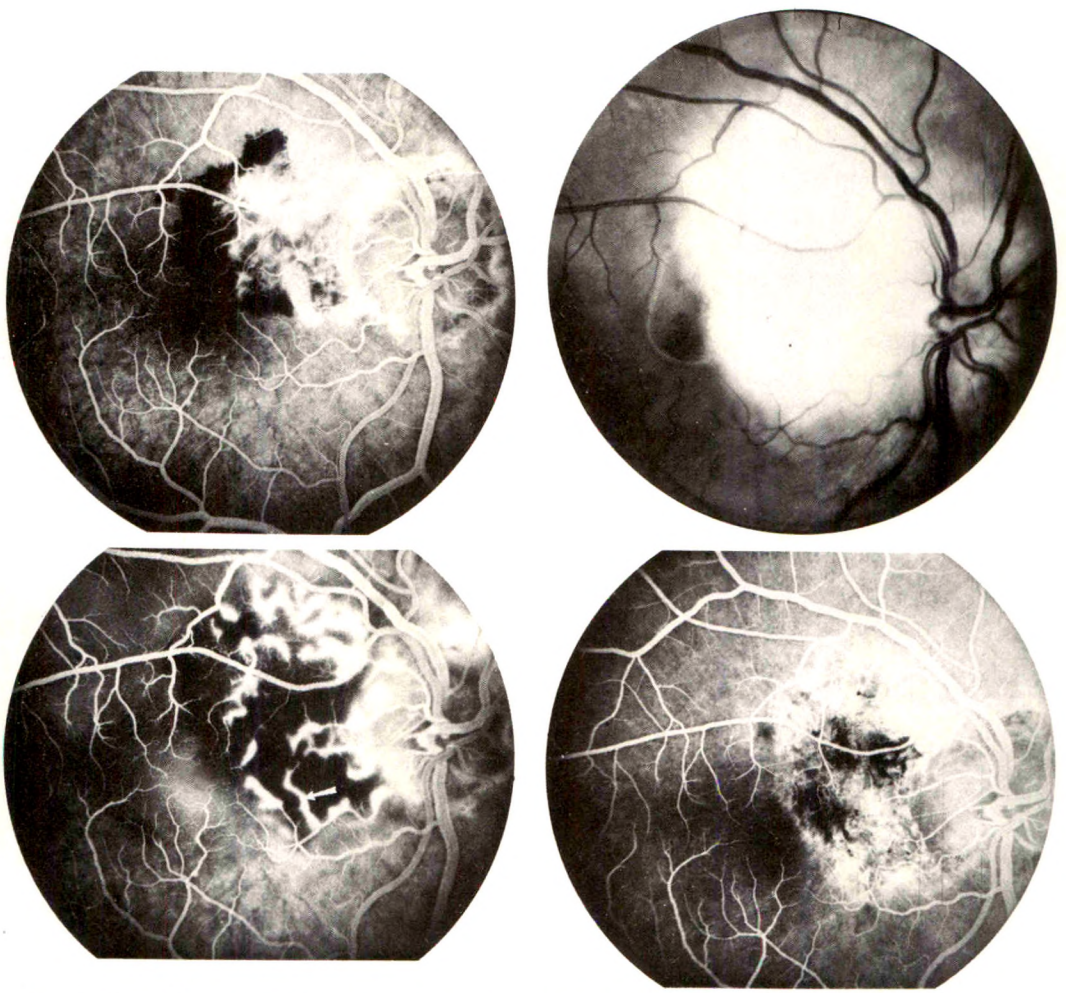

Fig. 5 (Cantrill and Burgess). Top left, Angiogram demonstrating a large zone of neovascularization temporal to the disk margin. Visual acuity is 6/30 (20/100). Top right, Red-free treatment photograph indicates confluent treatment of the entire neovascular network. Bottom left, Angiogram 24 hours after treatment demonstrates marked leakage from the retinal vessels (arrow) within the treatment zone. Bottom right, Angiogram five months later shows elimination of all neovascular tissue. Visual acuity is 6/7.5 (20/25).

ty of the photocoagulation lesions in treatment photographs. The results of Watzke and Leaverton's[10] early controlled study of photocoagulation treatment may have failed to demonstrate a treatment effect because insufficient treatment was given. For this reason, we have used the Zeiss xenon photocoagulator with its ability to give intense, confluent lesions with few exposures. Figure 5 illustrates the intensity of treatment we believe is necessary to eliminate subretinal neovascularization. Despite our efforts to treat all membranes heavily, we have found evidence of residual neovascularization in seven (37%) with subsequent failure in two (10%) because of extension of the membrane into the fovea. This failure rate demonstrates the difficulty in providing uniform intense energy to the neovascular membrane in areas of blood and fluid.

Late recurrence of neovascularization

after adequate treatment has not previously been stressed. Gitter and Cohen[9] reported one case reactivating from the border of a photocoagulation scar. Of our treated cases, four (21%) demonstrated recurrence six months or more after treatment when postoperative angiography had shown total elimination of the membrane. Development of neovascular membranes has been reported after photocoagulation treatment, particularly when small, intense lesions are used.[19] Conversely, we have found evidence of recurrent activity in eight (40%) of our untreated patients. One of these developed an active subretinal membrane from the border of an inactive scar during the course of follow-up (Fig. 3). Others have found recurrence rates of 4 to 25% in untreated cases followed up three to four years.[4,14] Therefore, recurrence need not be considered a consequence of treatment.

There are no controlled studies advocating treatment of peripapillary membranes in patients with ocular histoplasmosis. The significant percentage of fellow eyes with loss of central vision (ten, 29%) and the frequency of eyes with untreatable disease (six, 15%) emphasize the risk for visual loss. Of our treated patients, 12 (63%) maintained visual acuity of 6/12 (20/40) or better even though these membranes were closer to the fovea and demonstrated more serous and hemorrhagic detachment than our untreated patients. This represents a marked improvement over the course of untreated peripapillary membranes in a similar number of patients followed up by Schlaegel and Weber.[4] We believe that prolonged serous or hemorrhagic detachment of the fovea, documented progression of peripapillary neovascularization, and perhaps loss of central vision in the fellow eye are indications for photocoagulation. Conversely, many cases can be followed up without the use of photocoagulation, particularly if the membrane is more than one disk diameter from the fovea.

Summary

We studied 39 eyes with ocular histoplasmosis and peripapillary neovascular membranes for an average of 12 months. On the basis of clinical findings, 19 were selected for treatment with photocoagulation. Of the treated eyes, 12 (63%) had a visual result of 6/12 (20/40) or better. Of the 20 untreated eyes, six were clinically untreatable and 14 were electively followed up. All but one of the eyes electively followed up had a good visual result. Proximity of the neovascular membrane to the fovea was the most important prognostic factor in determining visual outcome. All eyes with membranes less than 1/4 disk diameter from the fovea lost central vision. All membranes greater than one disk diameter had excellent results. The indications for treatment were prolonged serous or hemorrhagic detachment of the fovea, documented progression of the membrane, and possibly, loss of central vision in the fellow eye from peripapillary disease. Residual and recurrent neovascularization were significant treatment complications.

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LEUKEMIC IRIS INFILTRATION

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Ocular involvement in leukemia is well established,[1] and histopathologically, the tissues most frequently affected are the choroid and the retina. Retinal and subsequent vitreous hemorrhages are the most common serious complications. Leukemic infiltration of the iris has been rarely reported.[1–10] Anterior segment changes, such as corneal infiltration and hyphema,[4] choroidal mass,[11] conjunctival lesions,[12,13] eyelid infiltration and exophthalmos,[14] and glaucoma,[15] although uncommon, can be the initial signs in a previously undiagnosed leukemic patient.

We describe herein leukemic iris infiltration and blood-streaked hypopyon in a 7-year-old boy, who underwent a diagnostic anterior chamber paracentesis; subsequently, he was treated successfully with radiotherapy.

CASE REPORT

A 7-year-old boy developed signs and symptoms of acute lymphocytic leukemia in March 1971. Bone marrow aspiration done at that time showed atypical lymphoid and monocytoid cells (Fig. 1). He was given vincristine and prednisone, and a bone marrow remission was induced in May 1971. The patient was maintained subsequently on methotrexate. Over a period of two years he developed four episodes of central nervous system involvement while his bone marrow disease was in remission. He was first seen by an ophthalmologist in December 1972, because of a two-month history of intermittent photophobia, redness, and tearing of the right eye. His visual acuity was R.E.: 6/15 (20/50) and L.E.: 6/6 (20/20). The right eye showed ciliary injection, thickening of the iris stroma, and rubeosis iridis. The anterior chamber had cells and flare (3+) and a yellow-white hypopyon. The fundus, including the optic disk, was unremarkable. The left eye was uninvolved. The intraocular pressures in both eyes were within normal limits by Goldmann applanation tonometry. Leukemic infiltration of the right iris was diagnosed and treated with cycloplegics and topical corticosteroids. Despite treatment, the boy's condition progressively worsened and bright red streaks developed in the hypopyon (Fig. 2). The intraocular pressure in the right eye increased to 30 mm Hg; the pressure in the left eye was within normal limits.

A diagnostic paracentesis was performed in February 1973, and 0.1 ml of anterior chamber fluid was removed. Cultures for fungi and bacteria were negative. Cytologic examination of the anterior chamber fluid using both Papanicolaou and Wright's stains revealed numerous mononuclear cells, occasionally in clumps (Figs. 3 and 4). Large atypical lymphoid and monocytoid cells were noted, with indented irregular nuclei, distinct nucleoli, and a small rim of blue cytoplasm without granules. These findings were compatible with leukemic involvement of the anterior chamber. After paracentesis, the hypopyon was decreased in size and thickening of the inferior iris could be seen (Fig. 5).

The anterior segment of the right eye was irradiated (325 rads in divided doses over four weeks). There was an immediate and significant decrease in photophobia after the first radiation dose (50 rads). During the course of treatment, the right eye was free of symptoms. The hypopyon, cells and flare in the anterior chamber, and leukemic iris infiltrate all progressively cleared. The intraocular pressure in his right eye also returned to normal. However, visual acuity improved only to 6/7.5-2 (20/25-2). During this period of ocular involvement, he was in bone marrow remission (hematocrit, white blood cell count, 40.4%; 6,300 with normal differential) and had no central nervous system involvement.

In March 1973, the patient developed headache and vomiting. A lumbar puncture revealed leukemic cells; however, the patient was still in bone marrow remission. He was given intrathecal methotrexate. Ocular examination in April 1973 showed an afferent pupillary defect, a pale optic nerve head, and a visual acuity of 6/12 (20/40) in the right eye. The left eye was unremarkable.

In September 1973, the patient received 600 rads to the right orbit and 1200 rads to his left testicle,

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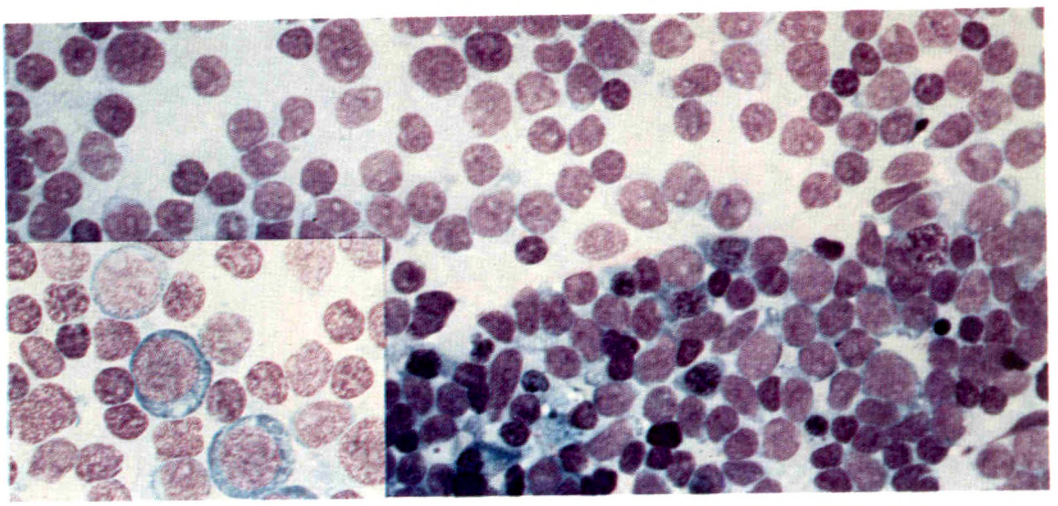

Fig. 1 (Zakka and associates). Bone marrow smear showing acute lymphocytic leukemia; inset, lymphoid and monocytoid cells (Wright's stain, x 100; inset, Wright's stain, x 400).

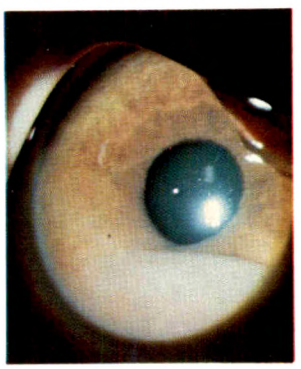

Fig. 2 (Zakka and associates). Slit-lamp photograph showing the blood-streaked hypopyon and hazy anterior chamber in the right eye.

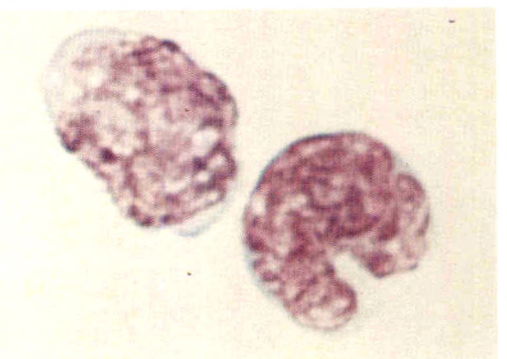

Fig. 3 (Zakka and associates). Anterior chamber fluid showing atypical lymphoid and monocytoid cells with indented nuclei, prominent nucleoli, and a thin rim of bluish cytoplasm (Wright's stain, x 400).

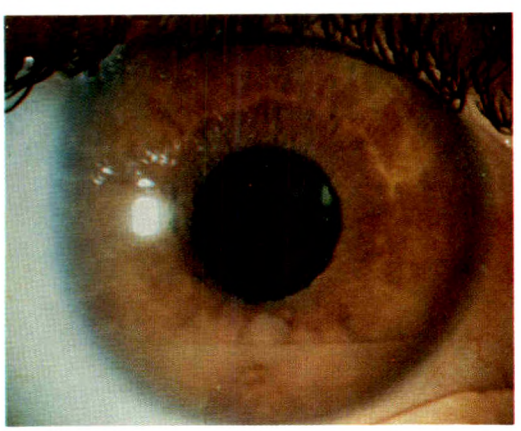

Fig. 4 (Zakka and associates). Anterior chamber fluid showing a cluster of cells with poorly preserved morphology (Papanicolaou stain, x 400).

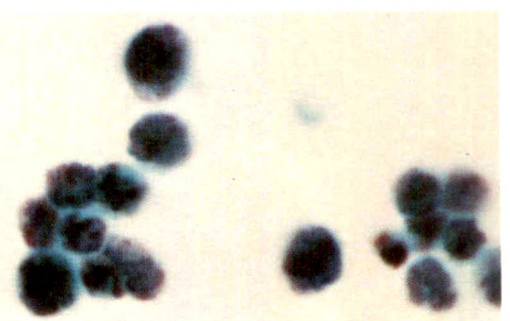

Fig. 5 (Zakka and associates). Slit-lamp photograph of anterior chamber immediately after paracentesis, showing white thinkening of the iris at the inferior pupillary margin and decrease in size of the pseudohypopyon.

which had developed infiltrates. In March 1974, he received whole brain irradiation because of central nervous system involvement. He did not improve and died in June 1974. No autopsy was performed.

Discussion

Leukemic involvement of the uveal tract on histopathologic examination appears primarily as hemorrhages, leukemic cell infiltrates, and dilated prominent blood vessels commonly filled with leukemic cells.[16] Hemorrhages in the uveal tract may be secondary to thrombocytopenia or invasion of vessel walls by leukemic cells, or both. Choroidal infiltration may be the first sign in leukemia, leading to visual loss and causing a diagnostic problem leading to enucleation.[11] Iris stromal infiltration is rare and usually involves areas adjacent to the iris root and sphincter muscle. In severe cases, there can be discoloration of the iris, which clinically appears as heterochromia.[3,7] This case shows that both hypopyon and hyphema can be of particular diagnostic value. Blood-streaked hypopyon has been described in myelocytic leukemia by Thomas, Rouhani, and Sawitsky[3] and in acute lymphocytic and lymphoblastic leukemia by others.[2,7] High intraocular pressure, found in our patient, was noted in six of eight previously reported cases of acute leukemia with anterior segment involvement.[2,5–8,17] The mechanisms causing high intraocular pressure could be infiltration of the trabecular meshwork by leukemic cells,[2] or formation of posterior synechiae, seclusion of the pupil, and pupillary block.[18] Glaser and Smith,[15] described a patient who had glaucoma. Because of a subsequent diagnosis of chronic lymphatic leukemia, they implicated limbal veins infiltration as a cause of glaucoma. Our case shows the beneficial effect of irradiation, which has been noted previously.[3,5,6,8,15] Ellsworth[19] pointed out that complications of such therapy have been overemphasized, particularly lenticular changes associated with radiation. Merriam[20] studied the cataractogenic effects of irradiation in groups of patients who received single-dose treatment, treatment in divided doses over three weeks to three months, and treatment in divided doses in periods greater than three months. He found that the minimum cataractogenic dose was 200, 400, and 550 rads, respectively.

In our patient, the relatively low dose of radiation (325 rads total, administered in divided doses over four weeks) carries little likelihood of cataract formation,[20] but it is effective in clearing leukemic iris infiltrates.

Optic disk pallor noted after the fourth radiation dose could be secondary to central nervous system involvement, glaucoma, or irradiation. Fishman, Bean, and Cogan[21] described optic atrophy in two patients with acute lymphocytic leukemia receiving chemotherapy (vincristine, cytosine arabinoside, and methotrexate) and cranial irradiation (2,400 rads). They postulated the possibility of potentiation or summation effects of radiation and drugs (vincristine) causing optic atrophy.[21] In our patient, the potentiation effect of drugs and irradiation is a possible, although unlikely, factor in the development of optic disk pallor. Of particular interest in our case is the value of anterior chamber paracentesis, which has not been discussed specifically in previous reports, although a diagnostic iridectomy and an aqueous aspirate have been previously performed.[2,3] The fluid obtained from the anterior chamber in our patient was processed by both the Millipore filter cytologic technique using the Papanicolaou stain and the classic Wright's stain done on a dried smear. We found the Wright's stain to be superior, as it provided more distinct cytologic details. Anterior chamber paracentesis might be indicated in a few patients with leukemia if an infectious cause of a hypopyon is considered, especially because leukemic pa-

tients are often immunologically compromised.

Usually, the systemic manifestations and diagnosis of leukemia are evident before uveal involvement, although rarely the uveal involvement may be the initial manifestation of the disease.[11] In our patient, leukemic iris infiltrates developed while the bone marrow was in remission, and the central nervous system was uninvolved. Juvenile xanthogranuloma, a benign dermatologic disorder, can have ocular complications, which include iris lesions, hyphema, and secondary glaucoma that may lead to blindness.[22] Anterior chamber paracentesis and cytologic verification in this disorder has been reported recently.[23] Because both acute lymphocytic leukemia and juvenile xanthogranuloma affect young children, anterior chamber paracentesis could be helpful in the differential diagnosis. Additionally, the increasing demand from radiotherapists for a tissue diagnosis before the initiation of treatment cannot be disregarded. In a clinical study of children suffering from acute leukemia, 52 of 657 children (9%) had ocular involvement.[24] Ridgeway, Jaffe, and Walton[24] discuss the adequacy of topical corticosteroids and radiation in anterior segment leukemic involvement. About 50% of children in hematologic remission develop central nervous system leukemia,[25] and an association between central nervous system and ocular involvement has been described.[3,7,24] This emphasizes the importance of an awareness of ocular complications, especially because local ocular irradiation can be effective in the treatment of leukemic infiltration of the uveal tract.

Summary

A 7-year-old boy with acute lymphocytic leukemia developed iris infiltration, blood-streaked hypopyon, and high intraocular pressure. A diagnostic anterior chamber paracentesis was performed, which provided a cytologic diagnosis. The aspirate was studied by both the millipore filter technique with Papanicolaou stain and a dried smear using the Wright's stain. Wright's stain provided more distinct cellular details. Irradiation of the anterior segment resulted in clearing of leukemic iris infiltration, hypopyon, and glaucoma.

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Fifty years ago this month in THE JOURNAL:

The reason why the treatment of so-called simple detachment of the retina is generally regarded as nearly hopeless may be largely explained by an insufficient knowledge of the fact that this accident is caused by a rent or tear of the retina, through which the liquid of the vitreous passes into the interretinal or retroretinal space. Most practitioners pay little attention to these holes in the retina, while others (e.g., W. Lister) admit that they are frequently to be found but believe that they make treatment practically valueless and therefore contraindicate any operation. Both views are equally wrong; the latter opinion, particularly, causing many curable cases to be neglected. It is just the discovery of the tear in the retina which affords the possibility of a complete cure, because the hole may then be closed by means of thermopuncture through the sclerotic. An operation of this kind being much more practicable and successful in recent cases than in older ones, it ought not to be delayed by attempts at other forms of treatment which are generally useless.

Professor J. Gonin, Correspondence
Am J. Ophthalmol. 13:63, 1930

CRYPTOCOCCAL CHORIORETINITIS

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Cryptococcosis is a chronic, subacute or (rarely) acute pulmonary, systemic, or meningitic infection caused by the yeast *Cryptococcus neoformans.*[1,2] Patients with cryptococcal meningitis frequently have ophthalmic complications such as papilledema, optic atrophy, or extraocular muscle paresis.[3,4] Although these complications are usually a reflection of the meningoencephalitis, rather than actual intraocular invasion by the organisms, endogenous cryptococcal chorioretinitis or endophthalmitis may sometimes occur. Published reports on intraocular involvement with cryptococcosis were recently reviewed by François and Rysselaere.[5] In some cases, the presumptive diagnosis has been made on clinical evidence without histologic confirmation of ocular involvement.[6,7] In other cases, histologic confirmation of intraocular cryptococcosis was obtained but a well-documented clinical correlation was not available.[8–10] In rare instances, fundus lesions have been observed clinically in eyes that were shown later to contain *C. neoformans.*[11–12]

We describe a patient with bilateral endogenous ocular cryptococcosis in whom the development of an early fundus lesion was shown with fundus photography, fluorescein angiography, and ultrasonography. The diagnosis was established histologically by enucleation of the blind fellow eye, and further substantiated by a good response in the remaining eye to systemic anticryptococcal therapy. The clinical and pathologic findings in this case suggest that endogenous ocular cryptococcosis is primarily a choroidal disease with secondary infection of the sensory retina. This contrasts to other ocular infections such as those caused by toxoplasmosis, herpes simplex, and cytomegalovirus, which produce a retinitis with secondary choroidal involvement.

CASE REPORT

A 41-year-old man was apparently well until 1963 when, at age 25 years, he developed grand mal seizures of unknown cause that were controlled with phenytoin. He had no further problems until November 1977, at which time he developed somnolence, impairment of memory, staggering gait, and weakness of the lower extremities.

He was admitted to a local hospital where two lumbar punctures revealed increased cerebrospinal fluid pressure and increased protein. Cultures of the cerebrospinal fluid for acid-fast bacilli and fungi were negative and an India ink preparation revealed no organisms. Computed axial tomography and carotid angiography revealed no evidence of a brain tumor, but there was symmetrical and severe dilatation of the ventricular system. The final diagnosis was acute obstructive hydrocephalus, probably secondary to an inflammatory cerebral disorder of undetermined cause. The patient was treated by insertion of a right ventriculoatrial shunt. His neurologic status gradually improved.

Because no specific cause was found, the diagnosis of sarcoidosis was considered despite normal chest x-rays. A transbronchial lung biopsy was performed about three weeks after placement of the shunt. Cultures were negative for acid-fast bacilli and fungi and histologic sections revealed mild pulmonary fibrosis and one area showed a possible noncaseating granuloma. Special stains reportedly revealed no bacteria or fungi.

The patient had no further problems until June

From the Oncology Unit (Drs. Shields and Augsburger), and the Uveitis Service (Dr. Wolkowicz), Wills Eye Hospital, Philadelphia, Pennsylvania; and from the Department of Pathology, University of Pennsylvania (Dr. Wright), Philadelphia, Pennsylvania. This study was supported in part by the Retina Research and Development Foundation, Philadelphia, and the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Inc. Presented in part at the AOA-AFIP Alumni Meeting, Washington, D.C., June 22, 1979, and at the Annual Meeting of the American Uveitis Society, San Francisco, Nov. 9, 1979.

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1978, when he developed intermittent episodes of blurred vision in the left eye. He was examined by one of us (M.I.W.) and a white fundus lesion of the left eye was noted that was considered consistent with a diagnosis of toxoplasmic retinitis. A serum indirect fluorescent antibody test was positive in a titer of 1:128 and conventional treatment with pyrimethamine and sulfonamides was initiated. The retinal inflammation gradually became worse and systemic corticosteroids were added to the regimen. The ocular inflammation persisted despite treatment.

In early September 1978, the patient developed increasing lethargy, general weakness, speech impairment, and severe ataxia. On Sept. 26, 1978, he was admitted to the local hospital in a comatose state. No nuchal rigidity was evident. A lumbar puncture revealed an opening pressure of 196 mm Hg, H_2O, and xanthochromic cerebrospinal fluid with a protein level of 1,000 mg/100 ml and a glucose of 10 mg/100 ml. Cell count of the cerebrospinal fluid revealed mild pleocytosis, with 65% neutrophils and 35% lymphocytes. Cultures of the cerebrospinal fluid for viruses, bacteria, and fungi, as well as India ink preparations for cryptococci were again reported as negative.

Repeat computed axial tomography revealed enormously dilated ventricules. Subsequently, the patient had a revision and readjustment of the ventriculoatrial shunt. The original tube was obstructed by numerous blood clots. After revision of the shunt, his neurologic symptoms slowly improved and the patient was discharged on Dec. 19, 1978 to be followed up as an outpatient. The left eye was reported as having no light perception at the time of discharge.

The patient was seen by one of us (M.I.W.) for follow-up examination on Feb. 9, 1979. A fundus lesion was discovered in the asymptomatic right eye at that time and the patient was referred to the Oncology Unit on Feb. 9, 1979, for further examination to exclude the possibility of a metastatic tumor to the eye. He still had some difficulty with gait, but was awake and mentally stable.

Visual acuity was 6/6 (20/20) in the right eye and no light perception in the left eye. Applanation pressures were 8 mm Hg in the right eye and near zero in the left eye. The right eye was normal to external and slit-lamp examinations and the findings were confined to the fundus. A yellow, deep fundus lesion measuring about 3 mm in diameter with overlying retinal telangiectasia and small hemorrhages was located 3 mm below the optic papilla (Fig. 1). The remainder of the fundus was normal and the vitreous was clear. The left eye had moderate conjunctival and episcleral injection, peripheral anterior synechiae, old granulomatous keratic precipitates, iris neovascularization, and a mature cataract (Fig. 2).

Fluorescein angiography of the right eye showed early leakage from the telangiectatic blood vessels overlying the lesion with progressive staining of the lesion in the late angiograms (Fig. 3). B-scan ultrasonography of the left eye showed numerous focal

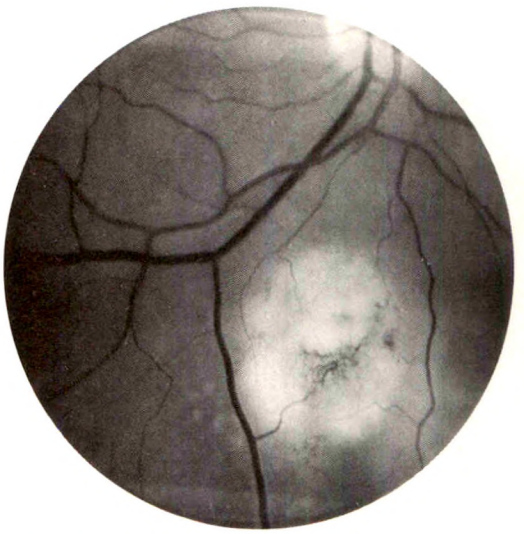


Fig. 1 (Shields and associates). Fundus photograph with 30 degree lens of asymptomatic chorioretinal lesion inferior to optic papilla in the right eye. The overlying vitreous contains no cells.

intraocular echoes compatible with inflammatory debris, but no retinal detachment or tumor was found. B-scan ultrasonography of the right eye showed an elevated lesion in the posterior pole with a smooth anterior border and acoustic solidity (Fig. 4).

Our clinical diagnosis was chorioretinitis in the right eye, and no light perception in the left eye, secondary to advanced chorioretinitis. We suspected a viral or mycotic cause, but atypical toxoplasmosis was also a consideration because of the positive *Toxoplasma* indirect fluorescent antibody titer. Clinically, however, the lack of vitreous cells and the failure to respond to antitoxoplasma drugs made that diagnosis unlikely. We also considered the

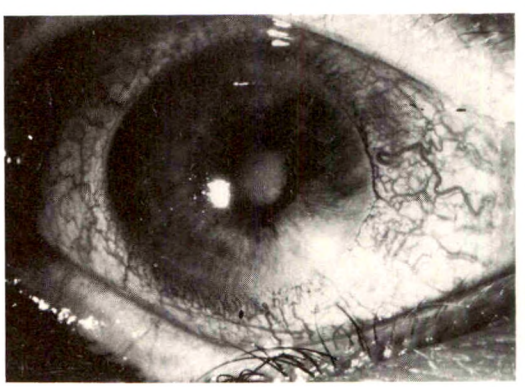


Fig. 2 (Shields and associates). External photograph of blind left eye showing epibulbar injection and cataract. Rubeosis iridis was present.

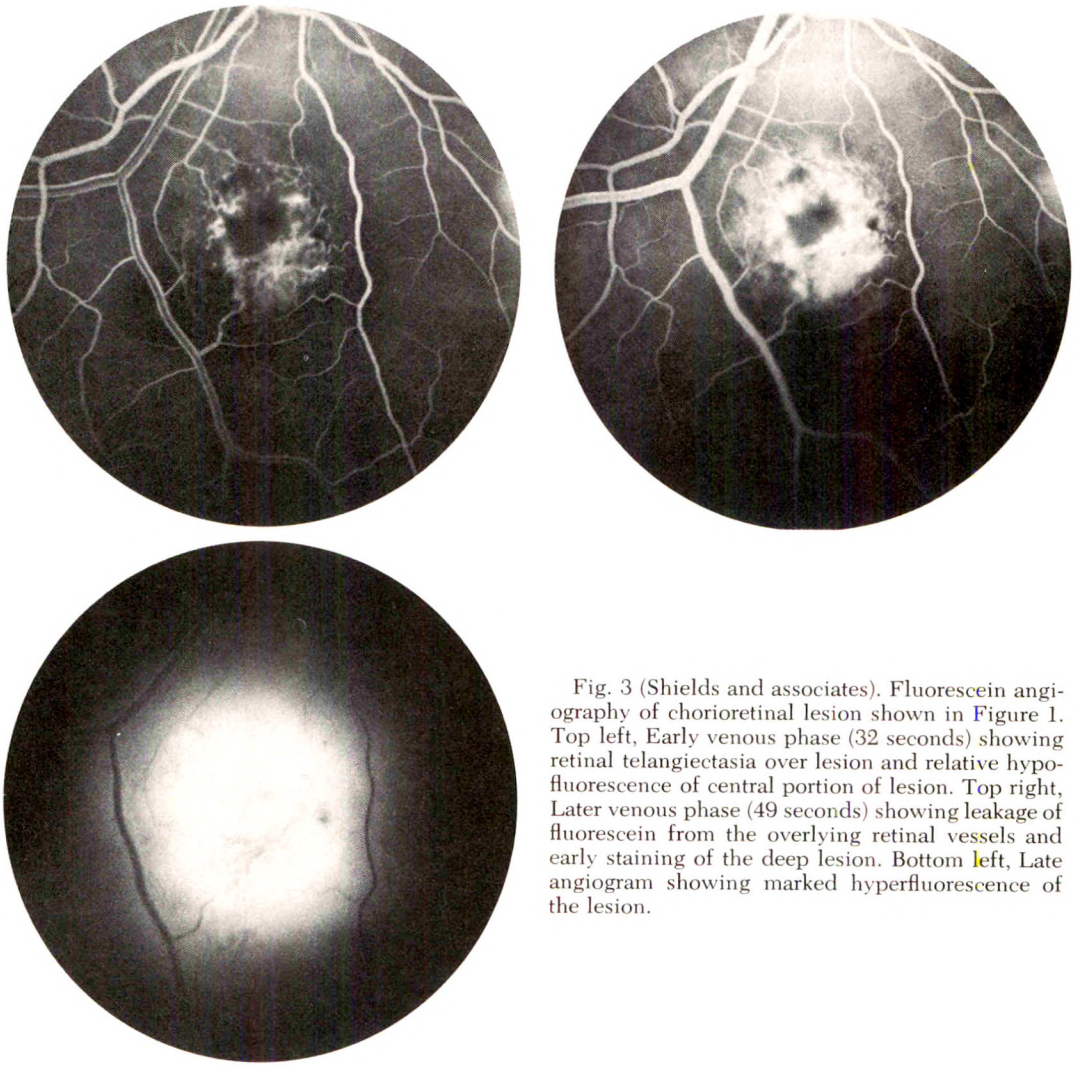


Fig. 3 (Shields and associates). Fluorescein angiography of chorioretinal lesion shown in Figure 1. Top left, Early venous phase (32 seconds) showing retinal telangiectasia over lesion and relative hypofluorescence of central portion of lesion. Top right, Later venous phase (49 seconds) showing leakage of fluorescein from the overlying retinal vessels and early staining of the deep lesion. Bottom left, Late angiogram showing marked hyperfluorescence of the lesion.

possibility of a mycotic embolus, perhaps from the infected shunt. The patient returned to the referring ophthalmologist, who specializes in uveitis, for further blood studies and immediate initiation of treatment. We also suggested the possibility of a diagnostic enucleation of the left eye.

The patient returned to his neurologist and did not see the ophthalmologist until Feb. 16, 1979, because he had developed painless visual loss in the right eye. He was referred to us for further consultation. His visual acuity in the right eye had decreased to 6/60 (20/200). The fundus lesion had increased in size and was associated with a surrounding retinal detachment with yellow precipitates in the subretinal fluid (Fig. 5). The fovea, which contained yellow intraretinal exudates, was detached by shallow subretinal fluid. The vitreous was still clear.

Because of progressive visual loss secondary to chorioretinitis of uncertain cause in the right eye, we

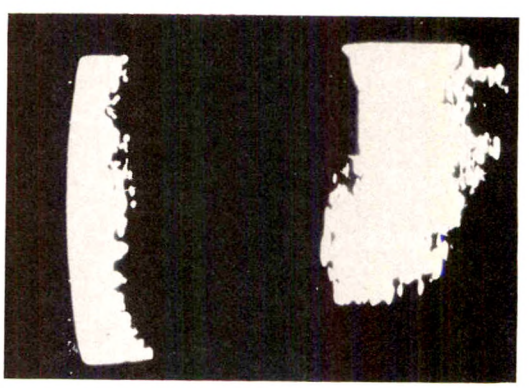


Fig. 4 (Shields and associates). Contact B-scan ultrasonogram of the right eye, showing elevated lesion with smooth anterior border and high internal reflectivity.

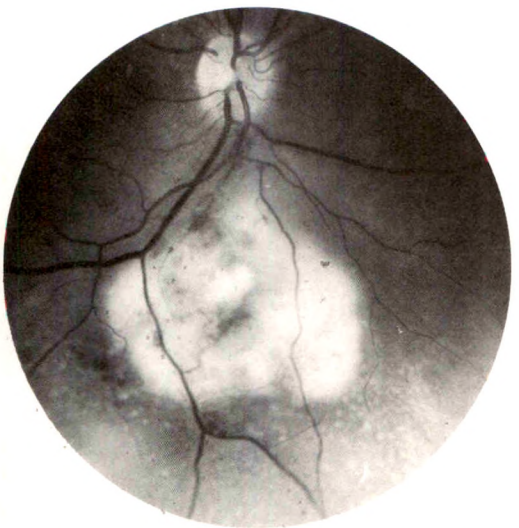
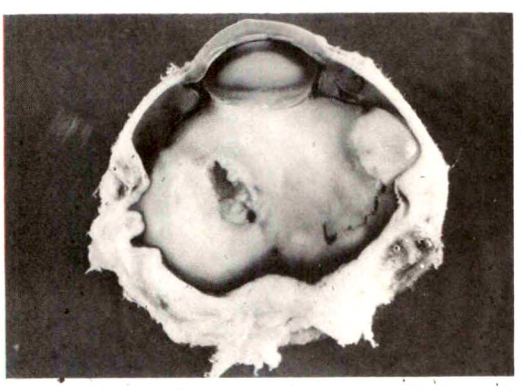


Fig. 5 (Shields and associates). Fundus photograph with 45 degree lens showing lesion in right eye seven days after initial visit. Note that the lesion has now extended across the large vein that was uninvolved in Figure 1. Focal yellow subretinal exudates are seen inferior to the lesion.

performed a diagnostic enucleation of the blind left eye. After an uneventful enucleation, we immediately opened the eye to obtain tissue for culture and electron microscopy. The eye was filled with a white mucopurulent substance that flowed out under pressure upon opening the globe. Immediate Gram stains of this material showed numerous yeast-like organisms. The PAS reaction showed spherical particles ranging from 5 to 15 μ in diameter and surrounded by a capsule 3 to 5 μ in width (Fig. 6). These organisms were characteristic of the genus *Cryptococcus.*

Therapy was initiated with intravenous amphoter-



Fig, 7 (Shields and associates). Photograph of sectioned left eye showing dense white material filling the globe. Note the anterior displacement of the cataractous lens (at top of photograph).

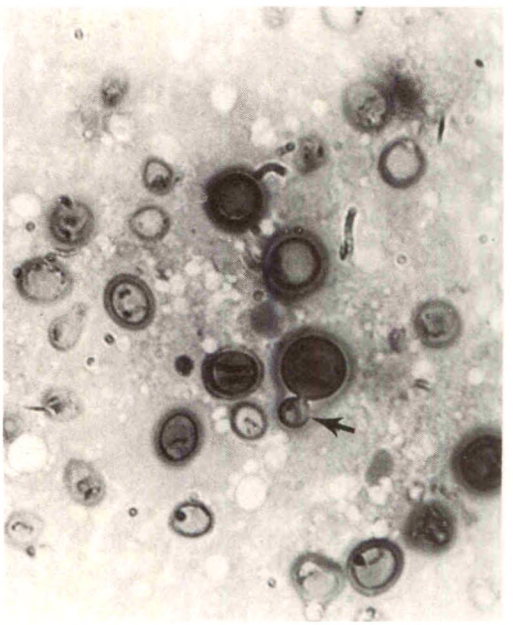


Fig. 6 (Shields and associates). Photomicrograph of organisms in the fresh smear of intraocular material (PAS, ×1,000). The organisms are compatible with *C. neoformans.* Note the budding form (arrow).

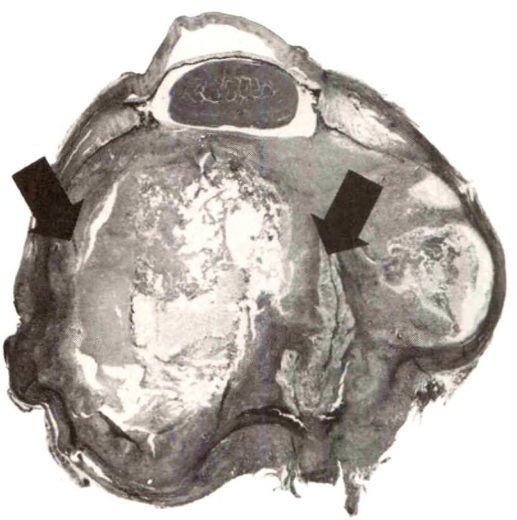


Fig. 8 (Shields and associates). Low magnification photomicrograph of sectioned left eye. Diffuse thickening of the degenerated choroid is evident (left arrow), a totally detached necrotic retina (right arrow), and an area of smooth homogeneous tissue posterior to the lens. The central necrotic material filling most of the globe is located in the subretinal space (hematoxylin-eosin, ×8).

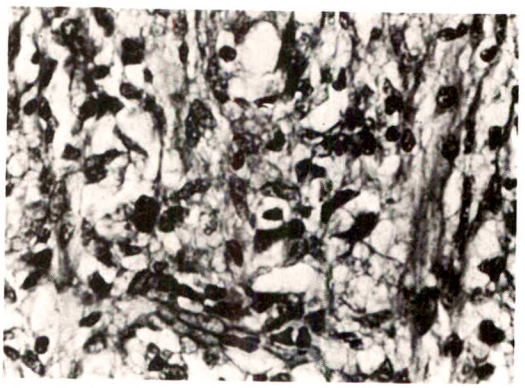


Fig. 9 (Shields and associates). Photomicrograph showing diffuse granulomatous inflammation at the level of the choroid (left arrow in Figure 8) (hematoxylin-eosin, ×200).

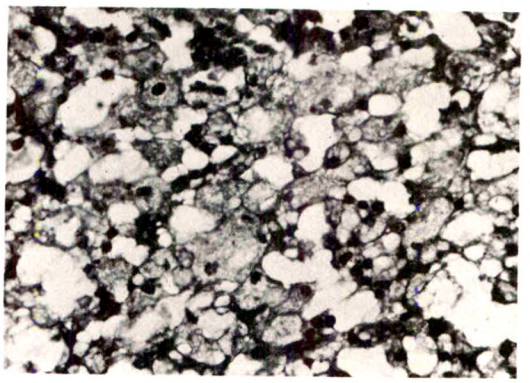


Fig. 10 (Shields and associates). Photomicrograph of area just inside the choroidal zone showing numerous large histocytes (hematoxylin-eosin, ×250).

icin B and 5-flucytosine orally. A repeat lumbar puncture revealed numerous lymphocytes, a protein content of 1,874 mg/100 ml, glucose of 12 mg/100 ml, and a cerebrospinal fluid cryptococcal antigen titer of 1:40 determined by the latex agglutination method. Cultures of both the intraocular material and cerebrospinal fluid grew *C. neoformans*. Small volume samples of cerebrospinal fluid initially did not yield the organism; eventually a 50-ml cerebrospinal fluid specimen became culture positive.

Gross examination of the sectioned eye showed replacement of the intraocular contents by thick white fluid behind a cataractous lens (Fig. 7). Low-power examination of the microscopic sections (Fig. 8) showed the residual retina to be detached and projecting forward from the optic disk. No identifiable retina was evident anteriorly. The degenerated and thickened choroid was largely replaced by chronic inflammatory cells and the subretinal space contained a heterogeneous eosinophilic substance.

Considerable variation in the patterns of inflammatory reaction within the globe was evident. The choroidal inflammatory reaction was characterized by a diffuse granulomatous process (Fig. 9) including epithelioid cells, lymphocytes, plasma cells, and occasional multinucleated giant cells. A zone of histocytes containing the fungal organisms was present between the choroid and the eosinophilic fluid (Fig. 10). Numerous free organisms and a few histocytes were present in the central ocular fluid. The abundant organisms showed active budding and stained with conventional fungal stains (Fig. 11). The dense tissue located behind the lens was mostly fibrous tissue with scattered plasma cells but rare organisms. Some fungi were present within the remaining recognizable retina but they were less concentrated than they were in the choroid and subretinal space. A few organisms were also found in the optic nerve head and in the perineural subarachnoid space.

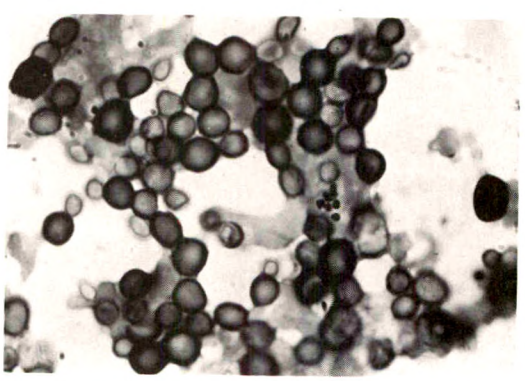


Fig. 11 (Shields and associates). Massive numbers of organisms with special stains for mucopolysaccharides. Note the budding forms (PAS, ×1,000).

The fresh material removed from the enucleated globe was placed in glutaraldehyde and prepared for electron microscopy. The organisms were characterized on electron microscopy by a small nucleus, electron-dense granular cytoplasm, and a thick cell wall. Each organism was surrounded by a capsule of fine, granular substance (Fig. 12). The organisms near the choroid were usually contained within large histocytes (Fig. 13) and those within the subretinal space were freely dispersed in the surrounding media (Fig. 12). The final histologic diagnosis was intraocular cryptococcosis.

The patient's visual and neurologic symptoms improved during the few weeks after initiating treatment. About six weeks later, he was discharged with a visual acuity of 6/21 (20/70) in the right eye and the macular exudate was showing progressive resolution. About six months later his visual acuity was 6/12 (20/40) and the macular exudate had resolved.

Discussion

This well-documented case of intraocular cryptococcosis is of interest for the

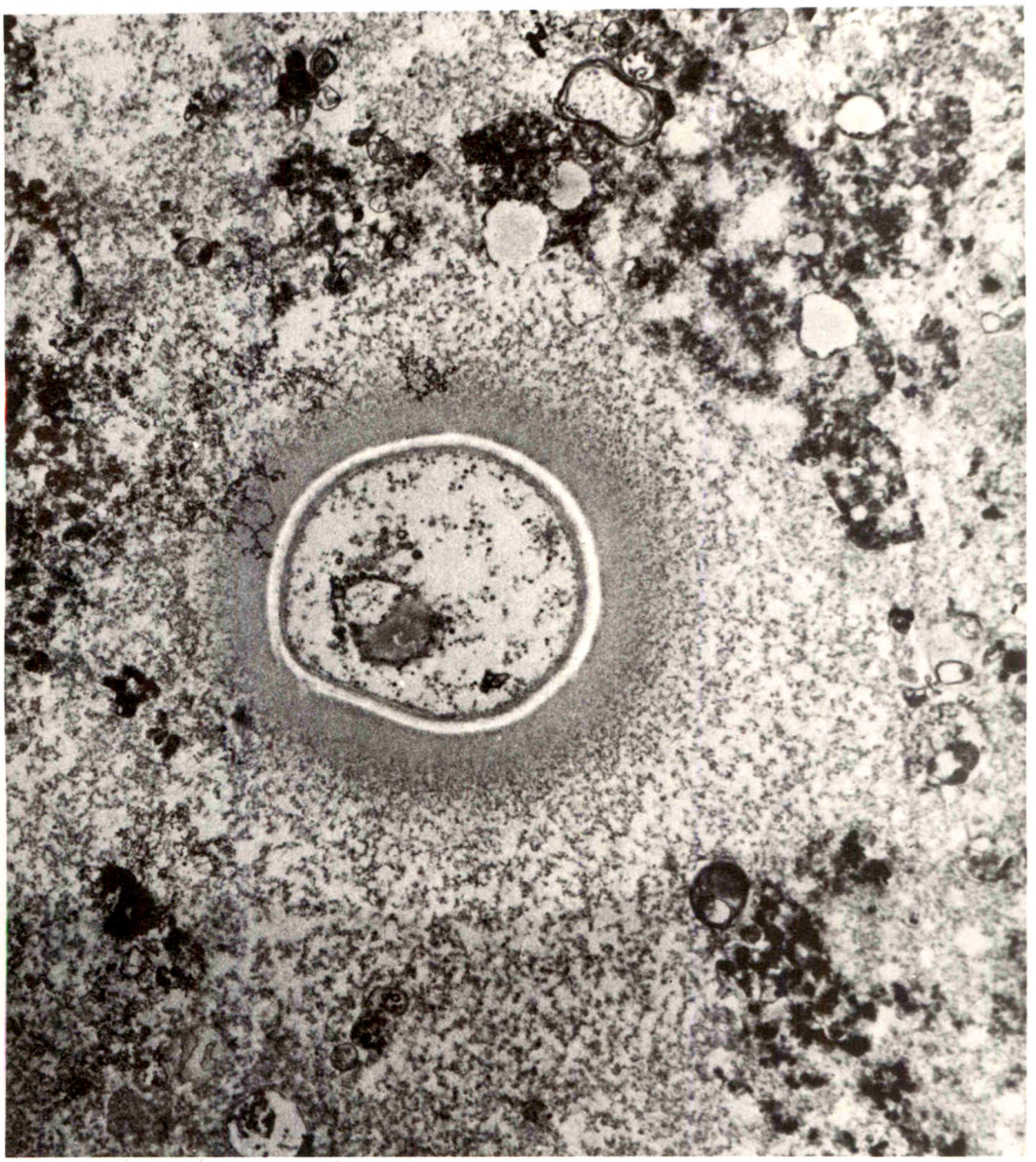


Fig. 12 (Shields and associates). Electron photomicrograph from central portion of subretinal space showing free cryptococcal organism. Note the distinct clear capsule and the capsule composed of fine granular substance that blends into the surrounding media (×6,940).

following reasons: (1) it shows that intraocular infection with opportunistic organisms may occur in a presumably healthy host who does not have a debilitating disease and who is not immunosuppressed; (2) it shows the value of diagnostic enucleation or biopsy of the blind eye in cases of bilateral progressive intraocular inflammation when the vision in the remaining eye is threatened; (3) it shows the ophthalmoscopic and fluorescein angiographic features that may be useful in differentiating cryptococcal chorioretinitis from other intraocular in-

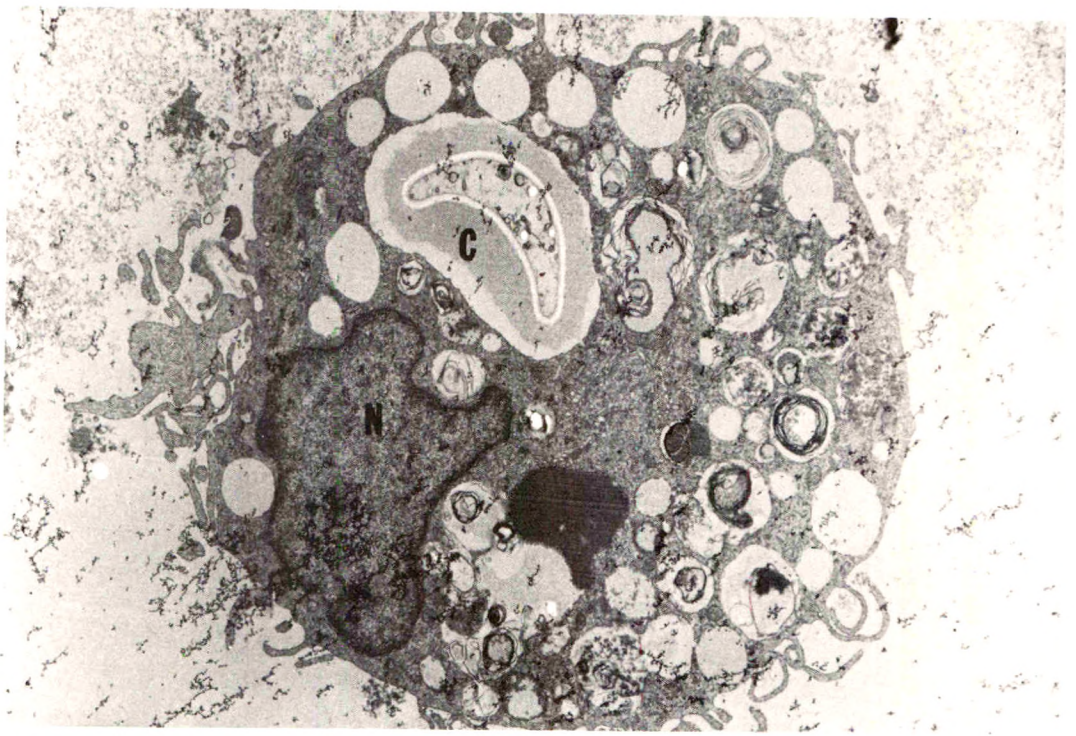


Fig. 13 (Shields and associates). Electron photomicrograph from region near choroid showing cryptococcal organism within a large histocyte. C indicates cryptococcal organism; N, nucleus of histocyte (×6,940).

flammatory processes such as toxoplasmic and cytomegalovirus retinitis.

In many reported cases, intraocular cryptococcosis has occurred as a result of cryptococcal septicemia associated with severe meningoencephalitis, often in patients who are debilitated or immunosuppressed. Underlying diseases such as malignant lymphoma[10] and systemic lupus erythematosus[12] have been recognized. Our patient had no underlying disease and was not immunosuppressed. Although he had idiopathic hydrocephalus, several cerebrospinal fluid examinations had reportedly failed to show cryptococcal meningitis. It was only after the organisms were shown in the ocular tissues that a repeat lumbar puncture established the diagnosis of cryptococcal meningitis.

The pathogenesis of the ocular infection in our patient is not entirely clear. On the basis of the usual sequence of events in such cases, the organisms were probably inhaled into the lungs, producing a subclinical pneumonitis. This probably led to hematogenous dissemination to the central nervous system and a chronic low-grade meningoencephalitis that produced hydrocephalus. The central nervous system reservoir or new subclinical pneumonitic episodes led to a recurrent septicemia that allowed the organisms to implant and proliferate in the vascular choroid.

Intraocular cryptococcosis may rarely occur by exogenous mechanisms. Recently a case occurred in which the infection was transmitted to the eye by a corneal transplant from a donor with systemic cryptococcosis.[13]

Our case raises the question as to the

value of diagnostic enucleation in cases where one eye is blind and the remaining eye is threatened by a similar inflammatory process. In our case the diagnosis could have been established by an intraocular biopsy with a vitrectomy instrument. Possibly, however, this would have seeded organisms into the orbit, producing a cryptococcal orbital cellulitis. Another problem with a biopsy by vitrectomy in intraocular inflammation is that in many cases the organisms are restricted to the retina and the vitreous contains mostly nonspecific inflammatory cells. This is particularly true in cases of toxoplasmosis, cytomegalovirus, and herpes simplex retinitis. In eyes that are blind, enucleation, rather than vitreal or retinal biopsy, provides a more reliable method of obtaining the involved tissue within the eye and establishing the diagnosis.

Finally, our case shows photographically and by fluorescein angiography the clinical features of an early case of intraocular cryptococcosis. Fundus contact lens examination and evaluation of the fundus photographs and fluorescein angiograms indicated that the initial lesion occurred in the choroid and secondarily involved the retina. This is in distinct contrast to intraocular infections with organisms such as *T. gondii,* cytomegalovirus and herpes simplex, which typically produce a retinitis characterized by opacification of the retina and cells in the overlying vitreous. The vitreous was clinically clear in our case. This differentiation is extremely important because treatment for toxoplasmosis, which often includes corticosteroids, may make cryptococcal infections worse. The problem was further complicated in our case by a positive serum indirect fluorescent antibody titer for toxoplasmosis. Toxoplasmosis rarely produces a choroiditis with sparing of the inner retina and vitreous as occurred in our patient. Other intraocular fungal infections, such as histoplasmosis, also primarily affect the choroid rather than the retina. This is in contrast to candidiasis, however, which often appears as a retinitis with secondary cells in the vitreous. Further evidence that intraocular cryptococcosis is primarily a choroiditis is provided by the case reported by Avandano, Tanishima, and Kuwabara.[10] Although their case lacked clinical correlation, the organisms were found only in the choroid and the retina was spared.

Summary

A 40-year-old man developed obstructive hydrocephalus of uncertain cause followed by bilateral intraocular inflammation, which was initially diagnosed as toxoplasmic retinochoroiditis. When visual acuity in the left eye decreased to no light perception and vision in the right eye was failing, a diagnostic enucleation of the blind left eye was performed. A diagnosis of cryptococcal endophthalmitis was established and the remaining right eye showed improvement after systemic anticryptococcal therapy.

Acknowledgments

Norman Schatz, M.D., Peter Savino, M.D., Larry Donoso, M.D., and Stanley Weinreb, Ph.D., assisted in the examination of this patient.

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Ophthalmic miniature

Long sight. In this species of vision the iris is habitually dilated, and not easily stimulated into contraction. Several varieties of this affection have been observed. Dr. Wells, in the Philosophical Transactions, relates the case of a young person who, from a permanent dilatation of the pupil, saw near objects with much difficulty and confusion, but remote bodies with singular accuracy. The power of moving the upper lid was completely lost. This dilatation of the pupil, which may be artificially produced by the application of belladonna, can be remedied by the use of convex glasses.

J. G. Millingen, *Curiosities of Medical Experience*
London, Richard Bentley, 1839

CLINICAL AND BIOCHEMICAL HETEROGENEITY IN GYRATE ATROPHY

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The test for genetic heterogeneity in human inherited disorders usually involves two considerations: (1) there may be a difference in enzyme activity or a related biochemical factor; and (2) one can assess variability in the clinical features of the abnormality, either among families or among unrelated persons.[1] The present study calls attention to at least two forms of gyrate atrophy, which can be so differentially characterized biochemically and clinically as to suggest the presence of genetic heterogeneity.

CASE REPORTS

Case 1—A 46-year-old woman of nonconsanguineous Welch parentage first noted decreased vision at age 11 years, which was improved to 6/6 (20/20) with myopic correction. At age 18 years, a diagnosis of retinitis pigmentosa was made on routine ocular examination. At that time, the patient was asymptomatic. Although the presence of early cataract was diagnosed at age 25 years, visual acuity remained stable until age 41 years, at which time the patient noted for the first time difficulty with night vision. At age 44 years, she first noted the onset of decreasing visual acuity that has been progressive. In January 1979, results of a general physical examination were normal. Ophthalmologic examination showed best corrected visual acuity was R. E.: 6/120 (20/400) with a correction of −4.00, and L. E.: 6/120 (2/400) with a correction of −2.50. Bilateral immature posterior polar cataracts with spoke-shaped extensions were noted, which were more advanced on the right. The Goldmann visual fields were 20 to 25 degrees in greatest diameter with the V_4e. Dark adaptation showed the best thresholds in the right eye were increased about 3.3 log units and in the left eye about 4.3 log units. Cone thresholds could not be measured. The electroretinogram (ERG) was extinguished and the electro-oculogram (EOG) showed abnormally low light-dark ratios bilaterally and the wave form was flat. On ophthalmoscopy, the media were hazy from the lens opacities, which were estimated to account for visual acuity of R. E.: 6/60 (20/200) and L. E.: 6/21 (20/70). The vitreous showed marked syneresis in each eye. The optic nerves were somewhat pale but not atrophic. Noteworthy was the characteristic scalloped border of degenerated retina and choroid encroaching on the posterior pole (Fig. 1). The retinal vessels were attenuated and the choriocapillaris was absent on fluorescein angiography.

Fasting plasma ornithine levels were 676 and

Fig. 1 (Kaiser-Kupfer, Valle, and Bron). Case 1. Left eye, The clarity of the photograph reflects the presence of lens opacities. However, the peripheral chorioretinal atrophy is shown.

From the Clinical Branch, National Eye Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Maryland (Dr. Kaiser-Kupfer); Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland (Dr. Valle); and the Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, England (Prof. Bron).

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640 μM. After ten days of high levels of vitamin B_6 (500 mg per day) with a normal protein intake, the plasma ornithine had decreased to 496 μM and after 14 days, to 480 μM. At these lower levels of plasma ornithine, no change in the ERG or EOG was noted. The activity of ornithine aminotransferase[2] in extracts of cultured skin fibroblasts was less than 2% of control values when assayed at both usual (16 μM) and high (500 μM) pyridoxal phosphate concentrations. On numerous occasions the electroencephalogram (EEG) showed low voltage background with intermittent alpha rhythm. Left midtemporal slow activity in both the waking and sleep states was evident.

Case 2—A 28-year-old woman of nonconsanguineous Irish parentage, was found to be myopic at age 11 years. On a routine examination at age 17 years, she was noted to have an unusual retinal appearance. An ocular examination was done and although the patient was asymptomatic, she was told of a defect in night vision. At present she does not complain of night blindness. When examined in March 1979, the best corrected visual acuity was R. E.: 6/7.5 (20/25) with a $-8.50 +1.50 \times 92$ degrees, and L.E.: 6/9 (20/30) with a $-6.75 +1.50 \times 80$ degrees. Early posterior polar lens opacities with fine spoke-shaped extensions were noted. There was moderate syneresis of the vitreous in each eye. Goldmann visual fields were 20 to 40 degrees in the greatest diameter with the V_4e. Final thresholds for rod function were normal and there was a slight increase in central cone thresholds. Ophthalmoscopic examination showed the characteristic findings of chorioretinal degeneration of gyrate atrophy (Fig. 2).

The ERG showed severely depressed rod and cone responses, more marked in the left eye, and the EOG showed abnormally low light-dark ratios bilaterally and the wave form was flat.

Plasma ornithine values averaged 488 μM over nine months (n=4, range, 488 to 572 μM). The activity of ornithine aminotransferase[2] in extracts of cultured skin fibroblasts was less than 2% of control values when assayed at both usual (16 μM) and high (500 μM) pyridoxal phosphate concentrations. A trial of high dosage vitamin B_6 was not undertaken at this time because the patient was three months pregnant. Results of general physical examination were normal. The EEG was considered normal although on two occasions it showed shifting slow irregularities during hyperventilation.

Fig. 2 (Kaiser-Kupfer, Valle, and Bron). Case 2. Composite of right eye shows chorioretinal atrophy with narrowing of vessels.

Discussion

The classic clinical findings of gyrate atrophy of the choroid and retina have been summarized by Takki and Simell in Finnish patients[3] and by others.[4–6] These findings include myopia in the first decade, night blindness of clinical significance in the second decade, cataracts of such severity that cataract extraction is often necessary in the third decade, and progressive visual impairment caused by pigmentary changes in the macula during the fourth and fifth decades. In contrast, our two patients had a diagnosis of myopia in the second decade. In Case 1 the patient did not have symptomatic night blindness until the fifth decade and in Case 2 the patient still does not have symptomatic night blindness at age 28 years. Although the patient in Case 1 had early cataracts described in the third decade, progression appeared to be slow so that it was only by the fifth decade that the lens opacities were thought to contribute possibly to a decrease in visual acuity. In Case 2 the patient still does not have significant lens opacities well into the third decade. Thus, although the clinical signs and symptoms are similar to those classically described in gyrate atrophy, the progression is much slower. Despite this difference in the time course of clinical symptoms, both of these patients exhibited the typical ophthalmoscopic appearance of the retina and choroid. This included the peripheral and midperipheral confluent areas of chorioretinal atrophy with scalloped borders, early obliteration of the choriocapillaris, dis-

turbance of the retinal pigment epithelium, narrowing of the retinal vessels, and pallor of the optic nerve.

In addition to the slower clinical course, these two patients also have levels of plasma ornithine lower than those classically reported in gyrate atrophy. Whereas the usual cases had plasma ornithine levels between 800 and 1,300 μM,[3–5] the levels in the two variant cases were between 452 and 676 μM. Similar lower levels were also described in one patient (Case 1) reported by Berson, Schmidt, and Shih[6] and in three patients (Cases 1 to 3) reported by Weleber, Kennaway, and Buist.[7]

Finally in one of our patients, the administration of high dose pyridoxine was associated with a 27% reduction in plasma ornithine concentration. The patient of Berson, Schmidt, and Shih[6] and the three patients of Weleber, Kennaway, and Buist[7] also had significant reduction of plasma ornithine during pyridoxine therapy. The more classic gyrate atrophy patients who have higher plasma ornithine levels (800 to 1,300 μM) do not decrease plasma ornithine in response to a trial of high dose vitamin B_6 administration.[3,5,6]

Despite the clinical and biochemical differences noted above in both, the usual and variant patients have had a marked deficiency of the activity of the enzyme ornithine aminotransferase in cultured skin fibroblasts.[6,8–10] In our experience, there has been no difference in the activity of this enzyme in those patients with high ornithine levels or in those with less striking hyperornithinemia. This finding was also reported by Berson, Schmidt, and Shih.[6]

Shih, Berson, and Mandel[11] reported an increase in ornithine aminotransferase activity as the concentration of vitamin B_6 in the enzyme assay system was increased 100-fold. Further study of this aspect is underway in our patients.

Heterogeneity is the rule rather than the exception in rare genetic disorders. Heterogeneity among gyrate atrophy patients has already been suggested by the observation that a few patients have a partial reduction in plasma ornithine in response to high dose pyridoxine.[6] The patients described in this paper have lower ornithines and milder clinical courses than those reported in patients with the classic gyrate atrophy. One also had a partial response to pyridoxine. These observations increase the evidence for clinical and biochemical differences among patients with gyrate atrophy. Additionally, recognition of the delayed clinical course in these patients must be a factor in assessing possible beneficial effects of either vitamin B_6 therapy or dietary therapy. Furthermore, the apparent association of reduced clinical severity with lower plasma ornithine values suggests a possible link between ornithine levels and the pathophysiological process.

Summary

Two patients had milder variants of the usual form of gyrate atrophy. Although the appearance of the chorioretinal degeneration was identical, the progression of the clinical signs and symptoms were slower with night blindness, cataracts, and decreased vision occurring at an older age. Additionally, the level of hyperornithinemia, although still increased above normal, was lower than that usually found in such patients (between 448 and 676 μM).

Additionally, one of our patients responded to high dosage vitamin B_6 with a 27% reduction in plasma ornithine. The difference in the quantitation of the increase in plasma ornithine, the difference in responsiveness to vitamin B_6, and the difference in the clinical consequences of this underlying biochemical abnormality, indicated a variant form of gyrate atrophy, suggesting the presence of genetic heterogeneity.

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DIAGNOSTIC MODALITIES IN CHOROIDAL MELANOMA

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The therapeutic efficacy of various modalities used in choroidal melanoma treatment is unknown.[1] Recently some investigators have suggested that enucleation may enhance rather than prevent the development of metastases.[2] In many ocular oncology centers patients with small choroidal melanomas and good vision are being serially examined without intervention until growth is documented.[1,3,4] As more patients with presumed choroidal melanomas are either serially followed up or treated with modalities other than enucleation, a number of management issues regarding the accuracy of diagnosis and measurements of tumor size in patients with pigmented choroidal mass lesions must be resolved. Among the most important questions are the following:

1. What are the sensitivity and specificity of clinical, ultrasound, and fluorescein diagnostic techniques?
2. What is the interobserver variation in the ophthalmoscopic measurement of tumor height and diameter?
3. What is the intraobserver variability of ophthalmoscopic and ultrasound tumor dimension measurements?
4. What are the correlations between ophthalmoscopic, ultrasound, and pathological measurements of tumor size?

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In an attempt to answer some of these questions, we have prospectively studied a group of 51 patients with histologically confirmed choroidal melanomas by assessing clinical, ultrasound, and fluorescein diagnostic factors in a masked manner.

SUBJECTS AND METHODS

Fifty-one consecutive patients who had undergone enucleation of a choroidal melanoma and 50 patients with simulating lesions who were examined here during 1978 and 1979 were included in this study. All patients had complete clinical examinations including indirect ophthalmoscopy, slit-lamp biomicroscopy with contact lens examination, Goldmann perimetry, and fundus drawings. The following clinical factors were assessed: vision, visual field, tumor height, tumor diameter, drusen, subretinal fluid, orange pigmentation, halo, degree of pigmentation, collar button configuration, and the presence of accessory nevi. Investigators who had not examined the patients clinically, interpreted the fluorescein angiographic studies, which were performed in a routine manner. Fluorescein angiographic factors analyzed included the following: tumor vessels, hot spots, leakage, cystoid edema of the retina, subsensory retinal pooling, window defect of the retinal pigment epithelium, blocked fluorescence, retinal vascular dilatation, pigment epithelial detachment, and drusen staining. Ultrasound examination included both B-scan and quantitative A-scan. Ultrasound evaluation and diagnosis were also performed in a masked manner by an investigator clinically unfamiliar with the patients. Ultrasound examination factors

examined included the following: tumor height, tumor diameter, orbital shadowing, retinal detachment, collar button configuration, increased blood flow, amount and pattern of sound attenuation, and choroidal excavation. Histologic examinations were performed using routine methods. All eyes were fixed in formalin, paraffin-embedded, and sectioned for light microscopy studies. Histologic studies were performed to assess the following factors: tumor diameter, tumor height, tumor location, anterior and posterior tumor margin, tumor cell type, degree of pigmentation, degree of necrosis, scleral extension, retinal invasion, break in Bruch's membrane, and tumor vascularity.

Patients were examined by at least four members of the oncology unit who independently established diagnosis, and in many cases measured both tumor elevation and diameter.

Clinical criteria for the diagnosis of a melanoma have previously been described.[1] Briefly, the presence of a lesion greater than 3 mm in elevation and 7 mm in diameter with subretinal fluid, orange pigmentation, a collar button configuration with visible tumor vessels, and an absolute scotoma on Goldmann perimetry suggested a malignant melanoma. On fluorescein angiography the presence of true tumor leakage and surface pooling with hot spots and obvious tumor vessels was considered diagnostic of a choroidal melanoma.[5,6] Ultrasound criteria diagnostic of a melanoma included the following A- and B-scan findings: choroidal excavation (B), retinal detachment (A and B), spontaneous pulsations (A), orbital shadowing (B), and a homogeneous attenuation greater than 50% (A).[7,8] Ultrasound patterns suggestive but not diagnostic of melanoma included the presence of choroidal excavation and an A-scan pattern with more than 50% homogeneous attenuation.

We assessed interobserver variability by comparing measurements of tumor height and diameter independently obtained in 21 patients by each faculty member with indirect ophthalmoscopy. Two of the patients were tested on more than one occasion without obvious growth documented either by ultrasound or fundus photography. The intraobserver variation was assessed by comparing the size estimation performed by one of us (D.H.C.) in patients who, on serial examinations, had no evidence of growth by clinical observation, ultrasound, and fundus photograph. Ultrasound reproducibility was determined by repeated scans of the same patients performed within a one-week interval.

The data were analyzed statistically by using a number of methods: Pearson product-moment correlation coefficient, Student's *t*-test, χ^2 analysis, Fischer's analysis, Kendall's Tau C analysis, and Kriskal-Wallis tests.[9]

Results

A number of clinical, ultrasound, and fluorescein factors were observed with a statistically significantly increased frequency in patients with pathologically confirmed choroidal melanomas vs simulating lesions ($P < .01$). The following clinical factors were observed more frequently in melanoma: subretinal fluid, orange pigmentation, and a collar button configuration; fluorescein factors were tumor vessels, leakage, and retinal dilatation; ultrasound factors were choroidal excavation, orbital shadowing, retinal detachment, collar button configuration, and increased blood flow. None of these factors were either pathognomonic or specific for a choroidal melanoma. All were also observed in patients with simulating lesions.

A clinical diagnosis of choroidal melanoma was made in 50 of 51 patients with histologically confirmed tumors. The

clinical diagnosis was deferred in one patient with opaque media.

In 32 (63%) cases the fluorescein angiogram was diagnostic for choroidal melanoma. In three (6%) it was equivocal (choroidal melanoma vs choroidal nevus), and in 15 (30%) it was nondiagnostic. All lesions were detected by ultrasound. In differentiating these choroidal masses, 41 (82%) patients examined with both A- and B-scan ultrasonography had patterns diagnostic for choroidal melanoma; three (6%) had findings suggestive of a melanoma; four (8%) had a diagnosis of a choroidal nevus. An ultrasound diagnosis of metastases was made in one case which was proven to be a choroidal melanoma on pathologic examination. In one patient with a blind eye and opaque media the diagnosis of a choroidal melanoma was made ultrasonographically; a subretinal hemorrhage was the only lesion observed on histologic examination.

The correlations of tumor dimension measurements are shown in Figure 1 and Table 1. Correlations between ophthalmoscopic-ultrasound, and ophthalmoscopic-pathology were statistically significant ($r \geq 0.61$) ($P < .001$). The inclusion of two cases with relatively diffuse melanoma decreased both the ophthalmoscopic and ultrasound correlation with pathology measurement of tumor diameter. In smaller choroidal melanomas (< 12 mm in diameter) the ophthalmoscopic estimation of diameter was more accurate than ultrasound. The ophthalmoscopic and ultrasound estimations of size were greater than those estimated on pathology. This may reflect the small degree of shrinkage observed with formalin fixation of the eye. The antero-posterior length of the globe was measured both by A-scan ultrasound and on gross examination of eyes containing tumors. Gross anatomic measurement of anteroposterior diameter was 3.6% smaller than the ultrasound estimation, which may be the result of shrinkage

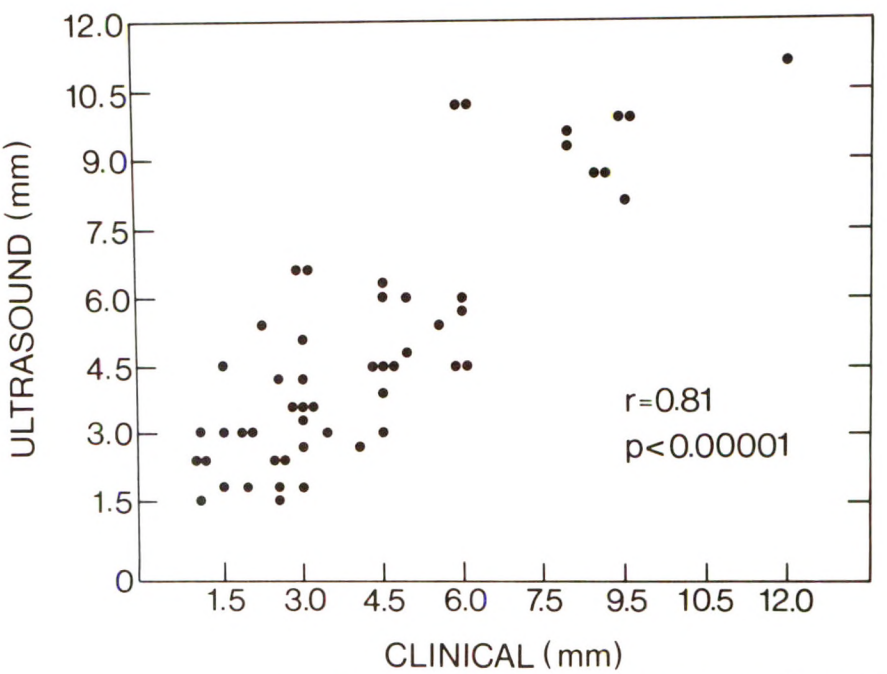

Fig. 1 (Char and associates). Measurement of choroidal melanoma height: ultrasound vs clinical determinations.

TABLE

OPHTHALMOSCOPY, ULTRASOUND, AND PATHOLOGY CORRELATIONS IN TUMOR DIMENSIONS*

	Ophthalmoscopy-Pathology	Ultrasound-Pathology	Ophthalmoscopy-Ultrasound
Diameter	0.71	0.69	0.61
Height	0.88	0.88	0.85

*P value < .01 (r value listed).

secondary to formalin fixation. The overall shrinkage of the globe, however, may be less than the shrinkage of the choroidal layer and the tumor.

A coefficient of variation was used to calculate the interobserver variability of tumor diameter and height measurements by indirect ophthalmoscopy in 21 patients. This was derived by dividing the standard deviation of the pooled measurements for a given patient by the mean measurement for that patient. The coefficient of variation for the interobserver diameter measurements was 19.4% with a standard deviation of 1.74 mm. The coefficient of variation for tumor height was 28.6% with a standard deviation of 1.23 mm. The data on interobserver variability are shown in Figure 2.

Intraobserver variation was more difficult to assess since a certain degree of observer bias could not be eliminated. This variation was observed in nine patients who were serially examined either at three-month intervals without change in fundus photographs or ultrasound measurements or examined within a one-

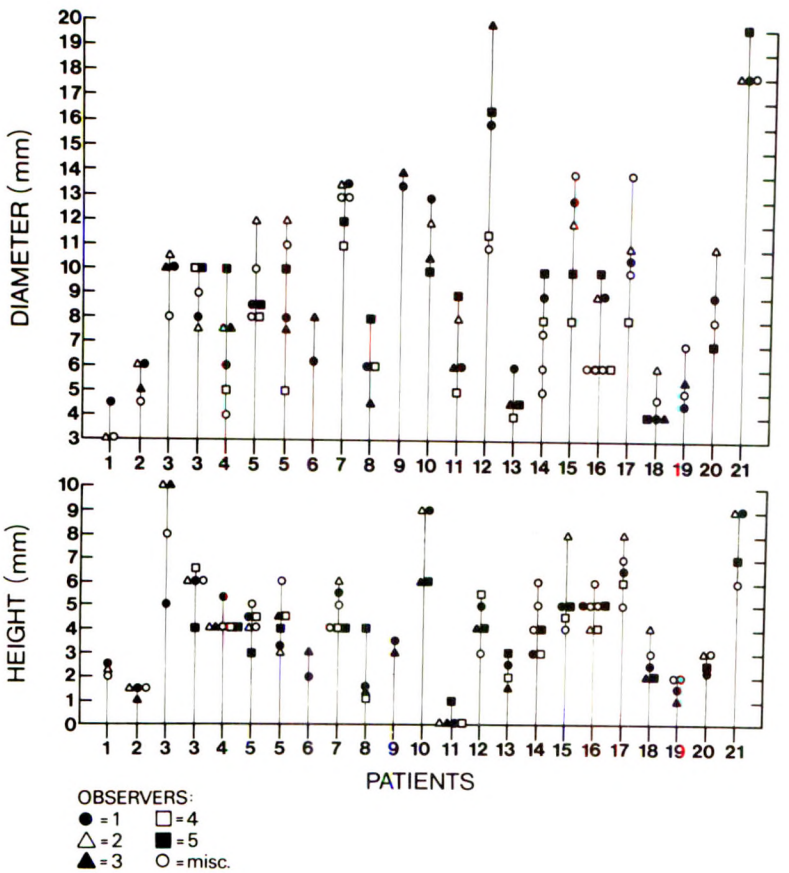

Fig. 2 (Char and associates). Tumor measurements performed by members of the Ocular Oncology Unit. Patients 3 and 5 were examined on two separate occasions.

week period. The clinical examination was done in a masked manner; there was a markedly less intraobserver vs interobserver variability in the nine cases measured (Fig. 3). The coefficient of variation was 7.9% for diameter and 21.3% for height. The standard deviations were 0.8 mm for diameter and 0.7 mm for height. The larger coefficient of variation for the height measurement in this group of patients was partially caused by the relatively small height of the lesions measured. Small differences in small heights resulted in a greater percentage of variation. A similar degree of intraobserver variation was noted in the four patients with large tumors who were examined many times during a one-week interval (Fig. 3).

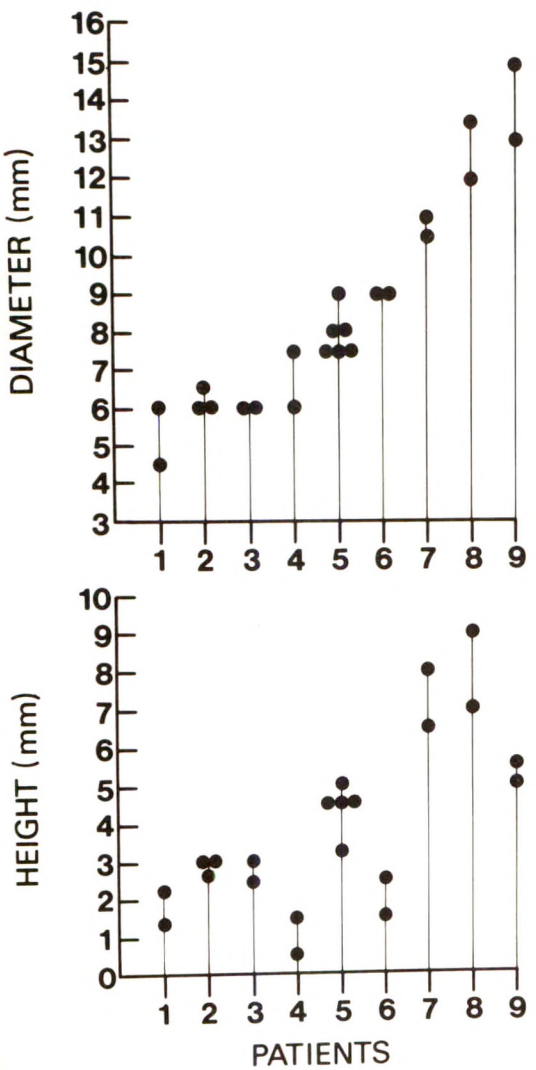

Fig. 3 (Char and associates). Intraobserver variability of tumor diameter and height in patients examined many times.

Ultrasound reproducibility of tumor height and tumor diameter was excellent. Twenty-six patients without evidence of growth either ophthalmoscopically or on fundus photography were ultrasonographically examined many times. The coefficient of variation for both diameter and height was 4%, the standard deviation for diameter was 0.41 mm and 0.20 mm for height. The most important cause of variation in ultrasound reproducibility was sampling errors. In lesions anterior to the equator it was often difficult to obtain reproducible positioning of the A-scan probe to measure the same area of the lesion. In these anterior tumors, there were some variations in tumor size measured by ultrasound. In one of these cases, the tumor height varied as much as 1.5 mm on different occasions within a one-week period. Most likely this was secondary to sampling errors since the anterior place lesions can be technically difficult to scan reproducibly, and different areas of the tumor may have been measured during different examinations.

In posterior pole lesions less than 12 mm in diameter, the ultrasound measurement of tumor diameter was excellent. In larger lesions, especially if these were peripheral and the tumors were less than 1.5 mm in height (that is, diffuse melanoma), the ultrasound underestimated the tumor diameter when compared with either ophthalmoscopic examination or pathology measurements.

Discussion

In ocular oncology centers the incidence of false-positive diagnosis of choroidal melanoma is less than 6%.[10–12] In our study only one of 52 eyes (2%) enu-

cleated because of the clinical diagnosis of melanoma, which was made by noninvasive techniques, had a benign simulating lesion.

Ophthalmoscopic examination was the most accurate diagnostic modality; choroidal melanomas were correctly diagnosed in all patients with clear media. In contrast, 45 (89%) cases examined by ultrasonography and 36 (70%) examined by fluorescein angiography were suggestive or diagnostic of melanoma. Previous studies on fluorescein angiography have demonstrated the diagnostic limitations of this modality.[5-6,13-15] The diagnostic accuracy of ultrasonography in this study is comparable to that which has been reported by some authors.[16-18] Various reports have suggested that 90 to 96% of choroidal melanomas can be correctly diagnosed with ultrasound; in this study the technique was suggestive of the diagnosis in 45 (89%); all 51 of the lesions were detected. Results of a radioactive phosphorus uptake test did not alter our diagnostic impression in any case examined.

Although the observed frequency of a number of diagnostic factors was statistically significantly increased in choroidal melanomas, none was either specific or pathognomic for a primary choroidal tumor. In this study only 15 (29%) patients with choroidal melanoma had orange pigmentation, and it was also observed in both benign and malignant simulating lesions. Previous studies have demonstrated the presence of orange pigmentation on clinical examination in 25 to 80% of choroidal melanomas.[19,20] Similarly, each of the fluorescein and ultrasound diagnostic factors was also observed in patients with lesions other than choroidal melanomas.

Many clinicians postpone therapy in patients with small tumors (less than 10 mm in diameter and 3 mm in height) until the growth is documented. Since therapeutic decisions are based on the documentation of growth, determining the accuracy of clinical and ultrasound measurement of tumor diameter and tumor height is imperative. The variability in clinical size measurements observed in this study makes it imperative to photograph all tumor margins in patients with small choroidal melanomas who are being serially evaluated for possible tumor growth.

There is inherent variability in all clinical measurements.[21] Since the initial studies in pulmonary roentgenology, the interobserver variability in measuring the same factor has frequently been demonstrated.[22] In ophthalmology, investigators have previously documented discrepancies in cup:disk ratio measured by trained observers.[23] In our study we observed that the measurement of tumor diameter and tumor height can vary among trained observers working closely together in the same unit. The standard deviation of interobserver measurement of tumor was 1.7 mm for diameter and 1.2 mm for height. Although there was slightly better agreement in small lesions, significant differences were still observed. Even among members of the same unit, relatively large (greater than 3 mm) discrepancies were occasionally noted (Fig. 2). For this reason, in most patients referred for a second opinion, we do not make a clinical judgment that growth has occurred until we have examined the patient on two separate occasions with ophthalmoscopy, ultrasonography, and photography of the tumor and its margins. Probably a change of at least 2 mm in tumor diameter and 1.5 mm in tumor height is necessary to establish tumor growth by clinical examination.

Because of inherent observer bias intraobserver variation was difficult to assess. To decrease this bias as much as possible, only the clinical measurements of those patients who were examined in a masked

manner and were either examined twice within a one-week period or examined serially without evidence of growth on clinical, ultrasound, or photographic examinations were included. Although this population tested for intraobserver variability was limited, the intraobserver variability observed in a given patient suggests that changes of less than 1 mm in either diameter or height on ophthalmoscopic examination are probably not significant.

The measurement of tumor height and diameter by ultrasonographic techniques, by using a combination of A- and B-scan is accurate in small lesions to the posterior pole. Unfortunately, these techniques have many limitations. Especially if the peripheral portion of a choroidal melanoma is less than 1.5 mm in thickness, ultrasound may underestimate the diameter of the lesions. Extensive subretinal fluid over the lesion may lead to an overestimation of tumor height. In certain locations, probably because of sampling errors, the B-scan (diameter) and A-scan (height) do not produce reproducible size measurements. In anterior lesions, especially in the temporal quadrant, exact repositioning of the ultrasound probe is difficult. In this study, some size discrepancies observed on serial ultrasound measurements of the same anterior lesion may have been secondary to sampling errors, which resulted in a discrepancy as great as 1.5 mm in tumor height. The variability of tumor diameter or height measurement by using ultrasound equipment in evaluation of posterior pole melanomas was less than 0.40 mm. In anterior lesions multiple measurements must be made, and possible variations should be kept in mind; in these lesions ultrasonographic differences of less than 1.5 mm in height may not always be significant.

The correlation among ophthalmoscopic, ultrasound, and pathology size measurements was good ($r > 0.61$; $P < .0001$). The correlation between height measurements made on clinical examinations was more closely correlated than tumor diameter (r values 0.86 vs 0.67). The measurement of tumor diameter was more difficult in lesions that were large or that had a large area of relatively flat tumor extension. This is partially due to the problem of estimating the size of a tumor which more than fills the field of a 20-diopter indirect ophthalmoscopy lens. We have also analyzed the overall ophthalmoscopic, pathologic, and ultrasonographic correlations (the sum of the differences in both diameter and height measurements). Ophthalmoscopic findings correlated with pathologic findings somewhat better than did ultrasonographic observations (r value 0.86 vs 0.79). This difference did not reach statistical significance. In those tumors that were less than 12 mm in diameter on pathologic examination, the ophthalmoscopic evaluation proved to be a more accurate measure of tumor diameter, whereas ultrasound examination more accurately reflected the tumor height. In patients being followed up without intervention for small melanomas, serial fundus photography, to assess changes in tumor borders, plays an integral role in our management of these patients. Since most tumors are too large for the field of a standard fundus camera, we did not assess the accuracy of fundus photographic measurement of tumor size.

Documentation of tumor growth is the most important factor used to determine which patients with small melanomas should be treated. In patients with small choroidal melanomas being serially examined without therapy, the possible in accuracy of tumor size measurement by ophthalmoscopy or ultrasonography should be considered.

Summary

We prospectively studied 51 patients with choroidal melanomas in a masked

manner to determine the accuracy of clinical, ultrasound, and fluorescein diagnosis as well as the accuracy of tumor size measurements. In patients with clear media, clinical diagnosis was the most accurate means of detecting a choroidal melanoma. There was excellent correlation between clinical, ultrasound, and pathology measurements of tumor size. In small melanomas, clinical examination was the most accurate means of measuring tumor diameter and ultrasound the most accurate method of measuring tumor height. Even with a trained ocular oncologist, there was a significant variability in tumor measurements on serial ophthalmoscopic examinations.

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EXPERIMENTAL OCULAR ANGIOGENESIS

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Ocular neovascularization occurs in the retina, as well as the iris, choroid, cornea, optic disk, ciliary body, and lens during the course of different ocular diseases. In some instances the neovascular process has been related to retinal ischemia.[1,2] Although the presence of a retinal angiogenesis factor has been speculated to be the cause of retinal neovascularization,[2,3] it has not been shown directly. Indirect evidence for the existence of a retinal angiogenesis factor includes the following: (1) the presence of disk neovascularization, retinal neovascularization, and rubeosis iridis in those conditions characterized by retinal ischemia; (2) the occurrence of disk neovascularization and rubeosis iridis at a distance from ischemic retina; and (3) regression of disk neovascularization, retinal neovascularization, and rubeosis iridis in certain cases after ablative photocoagulation of ischemic retina.

We describe herein an animal model in which direct evidence is shown that damaged vascular retina and other damaged vascular ocular tissues induce a vasoproliferative response at a distance. This neovascular response may be secondary to a diffusible heat labile, noninflammatory angiogenic factor.

MATERIAL AND METHODS

Intracorneal heterotopic autografts of rabbit retina were performed in New Zealand white rabbits weighing 2.7 kg. One eye of each rabbit was enucleated and the vitreous removed under sterile conditions, by using open-sky vitrectomy. Pieces of vascular peripapillary retina and retina from the relatively avascular periphery, each measuring 1.5 × 1.5 mm, were dissected under the operating microscope. The sections of retina were immediately inserted into corneal intrastromal pockets at the 6 and 12 o'clock positions (Fig. 1), previously prepared in the contralateral eye of the same rabbit, according to the technique of Gimbrone and associates.[4] The average distance from the limbal vasculature to the insert-

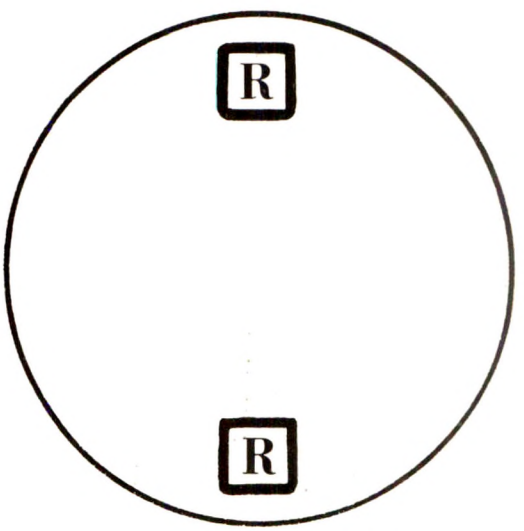

Fig. 1 (Federman and associates). Schematic diagram of retinal autografts (R) within the corneal stroma of the contralateral rabbit eye. Average distance from the corneoscleral limbus to the implants was 0.5 mm.

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ed retinal implants was 0.5 mm, with some sections implanted adjacent to the limbal vessels and the farthest being 1.5 mm from the corneoscleral limbus. Autografts of vascularized retinal sections boiled in water for five minutes were performed in the same manner.

Other ocular autograft tissues were also implanted into their contralateral corneas. These included iris, choroid, iris and choroid after boiling in water for five minutes, optic nerve, sclera, extraocular muscle, cornea, and conjunctiva.

Rabbits were observed with slit-lamp biomicroscopy daily during the first week after implantation and subsequently every other day for periods up to eight weeks unless they were killed earlier for histologic study. Anterior segment photographs were obtained when necessary. Anterior segment fluorescein angiography was performed at varying intervals after intravenous injection of 1.0 ml of 10% fluorescein. Selected eyes were enucleated for histopathologic correlation at intervals varying from four to 60 days. In 52% of eyes with vascular retinal implants, the new vessels growing from the corneoscleral limbus anastomosed with the vessels of the implanted vascular retina. Three to six weeks after anastomosis, a 1.5-mm^2 piece of V_2 carcinoma was implanted in a separate pocket 0.5 mm central to the vascularized retina in six eyes (Fig. 2). The same procedure was performed in one eye with implanted anastomosed iris. Vessel growth patterns after tumor implantation were observed with slit-lamp biomicroscopy every other day for a two-week period and fluorescein angiography was performed periodically.

RESULTS

Implantation of peripapillary vascular retina—In all eyes with implanted vascular retinal tissue there was minimal or no inflammatory response, as would be characterized by corneal edema and anterior chamber reaction. Limbal hyperemia was noted in quadrants adjacent to all intracorneal vascular retinal tissue the day after implantation. New vessels extended from the dilated limbal vessels into the cornea, toward the retinal tissue one to two days after implantation. The average rate of new vessel growth during the first week was 0.12 mm/day (Fig. 3). The vessels sometimes grew in a plane superficial to the retina, in which case they grew past the implant without contacting it physically, and regressed within a week. Histologic study four days after implantation (Fig. 4) showed degenerating retina, neovascular intracorneal vessels, and no evidence of intracorneal inflammation.

If the implant was placed at a distance greater than 1.0 mm from the corneoscleral limbus, the vessels did not reach the implant. A distinct slowing of vessel growth at about the end of a week was seen with subsequent regression after ten days of growth.

In 15 of 29 vascular retinal implants, new vessels originating from the limbal vasculature reached the implant (all at 1.0

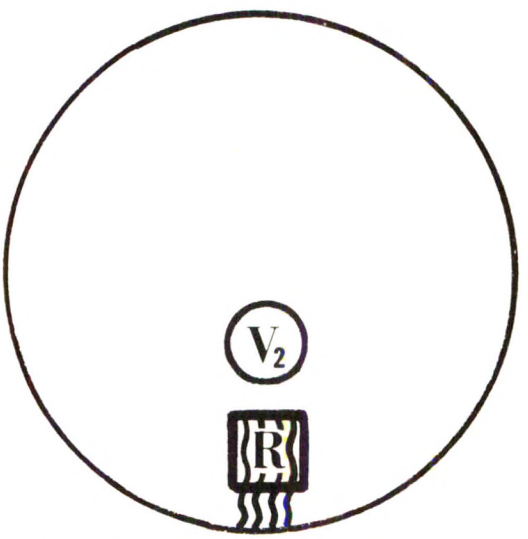

Fig. 2 (Federman and associates). Schematic diagram showing V_2 carcinoma (V_2) placed 0.5 mm central to the intracorneal vascularized retina (R).

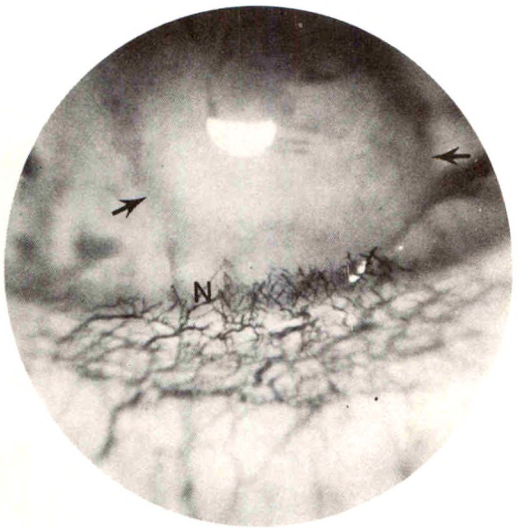

Fig. 3 (Federman and associates). Vascularized retinal autograft, the borders of which are defined by arrows, four days after implantation. There is a dense band of new vessels (N) of limbal origin growing toward the implant.

mm or less from the corneoscleral limbus), where an abrupt anastomosis with the intrinsic vasculature of the implant occurred (Fig. 5). The anastomosis was in all experiments associated with mild hemorrhage within the implant and a gradual development of intact circulation within the smaller vessels of the implant. About one week after anastomosis, the circulation within the implant stabilized, with resorption of the hemorrhage and regression of the limbal neovascular vessels to a few remaining channels feeding and draining the implant. This vascular system remained stable and unchanged for at least eight weeks of observation (Fig. 6) in the nine implants that were observed for this length of time. Implantation of two boiled vascular retinal specimens yielded only a minimal or no neovascular response.

Intravenous fluorescein angiograms of the retinal implant and limbal vessels varied during the course of the experiment. During the first week, as the limbal neovascular response to the vascular retinal implant occurred, there was marked, rapid leakage of fluorescein from the new vessels (Fig. 7). During the first week after anastomosis, there was not only leakage of dye from the connecting vessels between the corneoscleral limbus and vascular retinal autograft, but also leakage from the retinal autograft vessels. This leakage persisted for approximately one week after anastomosis. As the neovascular system between the corneoscleral limbus and implant regressed, leaving only a few feeding and draining vessels, the leakage of fluorescein from these vessels also diminished (Fig. 8).

Implantation of peripheral avascular retina—In five experiments the retinal implant consisted of peripheral anterior retina (without a visible vascular system).

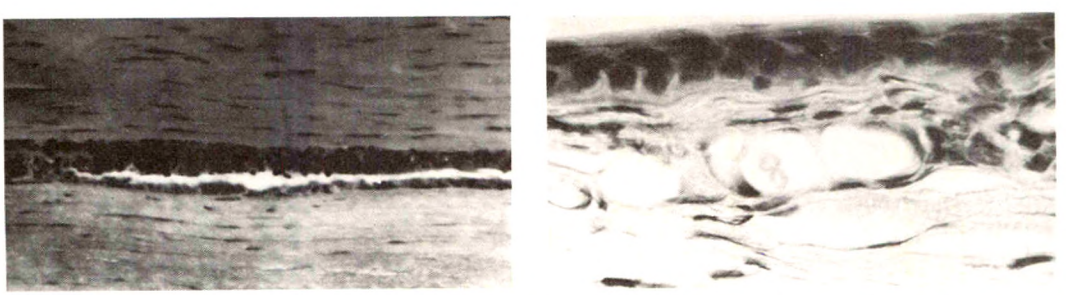

Fig. 4 (Federman and associates). Left, Intracorneal vascular retinal autograft shows degenerating retinal tissue and no inflammatory cells (hematoxylin and eosin, ×60). Right, New intracorneal vessels growing from the corneoscleral limbus toward the implanted vascular retina seen at left. Again, no inflammatory cells are present (hematoxylin and eosin, ×200).

Fig. 5 (Federman and associates). Same retinal autograft as in Figure 3 at eight days after implantation. Abrupt filling of some of the endogenous intraretinal vessels (white arrows) and a small hemorrhage (black arrow) within the autograft was evident. New vessels growing from the corneoscleral limbus are designated by N.

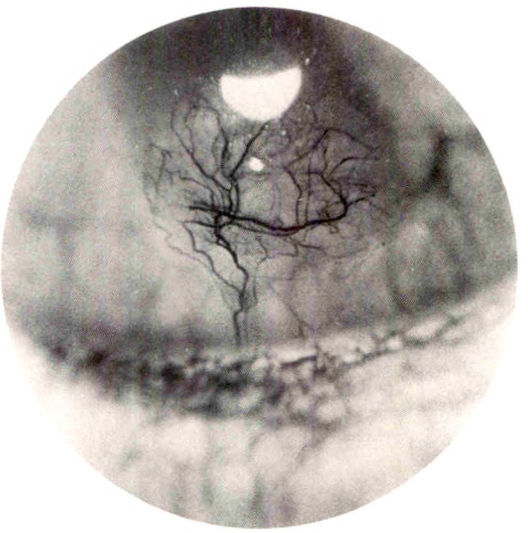

Fig. 6 (Federman and associates). Same retinal autograft as in Figure 5 at eight weeks after implantation. The retinal tissue is fully vascularized and the dense band of new limbal vessels has regressed.

The implants were placed at 0.5 mm from the corneoscleral limbus and in all cases an absent or minimal limbal neovascular response occurred, with vessels not growing more than 0.1 mm.

Implantation of other ocular tissues—The results of these experiments are summarized in the Table. Certain tissues induced a neovascular response, whereas others did not. The more vascular tissues

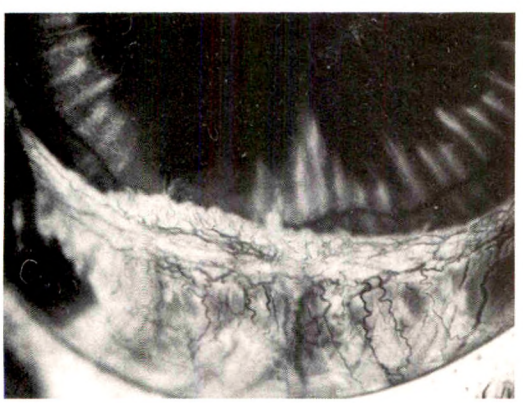

Fig. 7 (Federman and associates). Intravenous fluorescein angiography of vascular retinal autograft model at seven days after implantation, just before anastomosis between the limbal new vessels and autograft vessels. Intense leakage from the limbal new vessels is present.

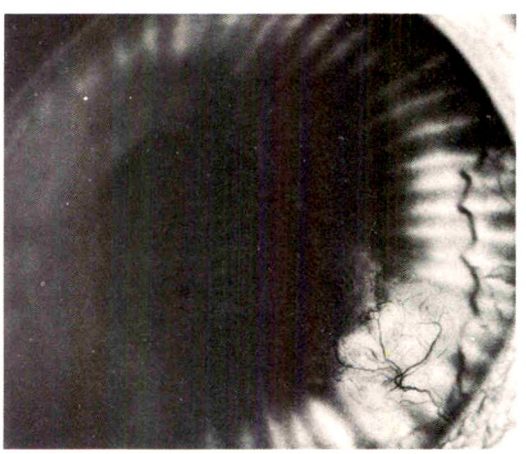

Fig. 8 (Federman and associates). Intravenous fluorescein angiography of retinal autograft shown in Figure 6 at eight weeks after implantation. There is, at most, minimal leakage from any vessels growing from the corneoscleral limbus or within the implant.

TABLE

RESULTS OF INTRACORNEAL IMPLANTATION OF RABBIT OCULAR TISSUES

Tissue	No. of Experiments	Limbal Neovascular Response*	Anastomosis	Inflammation†
Retina-vascular	29	3+	52%	None
Retina-avascular	5	0–1+	None	None
Retina (boiled)	2	0	None	None
Iris	2	3+	100%	Mild
Iris (boiled)	1	0	None	None
Choroid	2	3+	50%	Mild
Choroid (boiled)	1	0	None	None
Extraocular muscle	1	2+	??‡	None
Sclera	2	0	None	None
Cornea	1	0	None	None
Conjunctiva	1	2+	None	None
Optic nerve	1	3+	??‡	None

*On a scale of 0 to 4+, with 0 designating no response and 4+, a dense sheet of new vessels growing toward the tissue.

†Characterized by corneal edema and iritis.

‡No readily discernible abrupt anastomosis.

induced neovascularization, and with iris and choroid there was an abrupt anastomosis similar to that seen with the vascular retinal implants. This occurred soon after the limbal vessels reached the autograft tissue, approximately one week after implantation. Implantation of choroid and iris induced a short-lived, low-grade inflammatory response, which resolved after anastomosis took place. This inflammatory response was characterized clinically by corneal edema and iritis. Optic nerve and extraocular muscle induced a neovascular response, although a readily discernible abrupt anastomosis was not observed. Boiled iris and choroid, as well as sclera and cornea, induced no observable neovascular response.

Carcinoma (V_2) induced neovascularization from intracorneal implants—In these experiments (five with implanted retina and one with implanted iris), the vascular system of each autograft was stabilized and observed for four weeks before intracorneal implantation of V_2 carcinoma was performed. Fluorescein angiography before tumor implantation showed minimal or no leakage of dye from the vasculature of the autografts (Fig. 8). In all cases a similar specific response was noted in the vasculature of the implants beginning three to five days after the implantation of V_2 carcinoma. Individual vessels dilated and perfusion of the vasculature of the implant apparently increased (Fig. 9). This was followed by new vessels developing from the edge of the autograft closest to the tumor (Fig. 10). Marked leakage of fluorescein occurred early from all the vessels of the autograft, but it was more intense at the edge closest to the V_2 carcinoma, where the neovascularization originated (Fig. 10). The new vessels grew toward the V_2 carcinoma, connecting with it in seven to nine days.

DISCUSSION

Folkman and associates[5] proved the existence of a tumor angiogenesis factor. The presence of this diffusible factor, which elicits blood vessel growth toward a tumor to provide nourishment for exponential growth, has been shown in many human tumors.[6] Evidence for the exis-

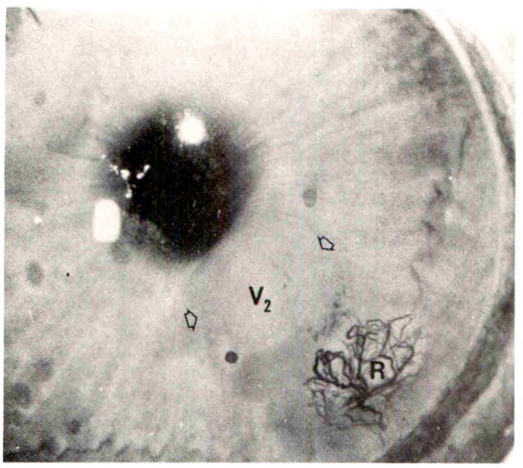

Fig. 9 (Federman and associates). Vascularized retinal autograft (R) and V_2 carcinoma (V_2), the borders of which are delineated by arrows, three days after implantation of the carcinoma. Vessels within the autograft are dilated, as compared to Figure 6.

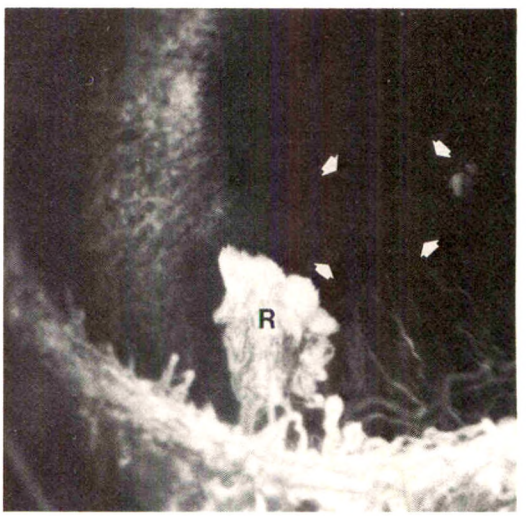

Fig. 10 (Federman and associates). Intravenous fluorescein angiography of this vascularized retinal autograft (R) four days after implantation of V_2 carcinoma (boundaries of which are delineated by arrows). There is leakage of fluorescein from all vessels within the autograft, most intense along the border adjacent to the carcinoma.

tence of an epidermal angiogenic factor has also been reported.[7]

The results of our experiments strongly suggest the presence of a diffusible, heat-labile factor in vascular retina and other vascular ocular tissues, which is capable of inducing a noninflammatory neovascular response.

Neovascularization may be associated with inflammation[8]; however, in our experiments this was clinically and histologically apparent, and minimal, with only choroidal and iris implants. The inflammatory reaction was short-lived and disappeared completely after the anastomosis took place.

By clinical and histologic criteria, the neovascular response seen with the vascular retinal implants was not associated with inflammation. The response was distance-related, suggesting the presence of a diffusible factor from the implant. The regression of the limbal neovascular response after anastomosis suggests that the implant stopped releasing the factor once a blood supply was established. However, possibly the cells of the vascular implant were so severely damaged by this time that they ceased releasing a factor.

Ischemic and degenerating tissues appear to be an inciting factor of neovascularization in our model. Implanting a highly vascular tissue, to which the blood supply has been severed in the avascular cornea, must create an extreme state of ischemia in the implanted tissue. Because tumor angiogenesis factor is most readily obtainable from lysed cells,[9] perhaps the proposed angiogenesis factor that we have observed is released from cells that have had cell membrane damage secondary to transplantation and ischemia.

The ocular tissues that induced neovascularization in our animal model all had a rich vascular supply. Possibly the blood vessels themselves may be the tissue source of an angiogenic factor. Teleologically, the hypothesis is appealing that damaged vessels have an intrinsic ability to regenerate or call for help from adjacent vessel systems. However, the tissue microenvironment surrounding vessels may also play a role, as has been hypothe-

sized with vessel growth in skin[7] and developing retina.[2]

The angiographic evidence of vessel dilatation and leakage seen from the intracorneal new vessels in these experiments correlates well with the fluorescein findings seen in patients with a variety of diseases that induce neovascularization of the retina, choroid, and iris. In diabetic retinopathy, early findings such as vascular dilatation and areas of papillary nonperfusion are seen, in addition to shunt vessels, microaneurysms, hemorrhages, and exudates. Often the vessels along the edge proximal to the areas of nonperfusion show early leakage with fluorescein. These vascular changes in the diabetic may not be sufficient to restore adequate perfusion. Subsequent continued secretion of an angiogenesis factor from areas of ischemic and damaged retina finally may result in capillary endothelial cell proliferation (neovascularization) with vessels that leak fluorescein. Neovascularization frequently develops at the edge of or near areas of retinal nonperfusion.

Our findings vary from those of Folkman and Tyler,[10] who stated that intracorneal adult rabbit isograft tissues (that is, heart, kidney, and thyroid) do not stimulate neovascularization, even when physically adjacent to the corneoscleral limbus. Embryonic tissues, however, do anastomose in about two days if placed adjacent to the corneoscleral limbus. Therefore, they propose that only neoplastic tissue can induce a neovascular response at a distance. We do not know the reason for this variance, although Folkman and Tyler[10] did not examine ocular tissue.

However, our experiments show that damaged vascular retina and other damaged vascular ocular tissues induce a vasoproliferative response at a distance. This neovascular response may be secondary to a diffusible heat-labile, noninflammatory angiogenic factor.

Summary

In 29 experiments, vascular autologous retina from the contralateral rabbit eye was implanted into corneal pockets in New Zealand white rabbits. The implants induced a neovascular growth of limbal vessels that anastomosed with the vessels of the implant in 15 of the cases. Implantation of vascular autologous iris, choroid, optic nerve, extraocular muscle, and conjunctiva also induced neovascularization. Avascular peripheral retina, cornea, and scleral implants did not cause a neovascular response, nor did boiled vascular retina, boiled iris, and boiled choroid. Neovascularization from the retinal and iris intracorneal implants was induced by V_2 carcinoma.

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GRAY CRESCENT IN THE OPTIC NERVE HEAD

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Increased pigmentation along the margin of the optic nerve head in some cases defines a choroidal ring or crescent that is exposed where retinal pigment epithelium does not reach to disk margin. This is usually caused by oblique insertion of the optic nerve, as in myopia.[1] In other cases, a darker pigmented ring or crescent results from a proliferation of retinal pigment epithelium or from a lip of pigment epithelium, Bruch's membrane, and choroid extending over the scleral foramen.[1] Irregular pigmentation may also result from juxtapapillary choroiditis or choroidal degeneration.

We describe herein the importance and clinical features of another pigmented crescent of the disk, which differs from the previously mentioned types in that it appears to be located within the substance of the optic nerve head.

CASE REPORT

A 47-year-old black man was referred here for evaluation of glaucoma. His visual acuity was R.E.: 6/6 (20/20) with +0.50 and L.E.: 6/6 (20/20) with +0.25. Applanation intraocular pressures were R.E.: 32 mm Hg and L.E.: 31 mm Hg. Results of external and slit-lamp examinations were within normal limits, and the anterior chamber angles were open and normal by gonioscopy. The optic nerve head cups were large, but symmetrical (Fig. 1). Wide, slate-gray crescents extended along the temporal and inferotemporal margins of each disk, with darker pigmentation peripheral to the gray crescents. The cups extended to the gray crescent in each eye giving the appearance of inferotemporal thinning of the neural rims. Visual fields were normal.

Fluorescein angiography of the optic nerve heads (Fig. 2) revealed hypofluorescence in the region of both the gray and the darker pigmented crescents. However, in the early filling phase, vessels were seen in the area of the gray crescents that appeared to be contiguous with vessels in the central portion of the disks. In the late phase, uninterrupted hyperfluorescent rings surrounded the disks and the gray crescents. Based on these fluorescein angiographic observations, we believe that the gray crescents lay within the substance of the optic nerve heads. Therefore, the neural rims were interpreted as being even, suggesting that the optic nerve head cupping was physiologic.

MATERIAL AND METHODS

The case reported (Case 1 in the Table) showed the clinical importance of the gray crescent in the optic nerve head. I examined a consecutive series of 28 additional patients with this type of pigmented crescent. Many patients had been referred for evaluation of possible glaucoma. The examination included Hruby lens evaluation and fundus photography of all disks. Fluorescein angiography of the optic nerve heads was performed on five patients.

RESULTS

There were 17 females and 12 males in the study, ranging in age from 10 to 69 years, with an average age of 35 years; 25 patients were black and four were white. Twelve of the black patients were from a series of 100 consecutive blacks who were examined to investigate the frequency of the gray crescent in this race. The four white patients with gray crescents all had dark complexions and one had ocular melanosis.

Of the 58 eyes, 30 were myopic. Spherical equivalents in these 30 eyes ranged from −0.25 to −5.25 and averaged −1.91. All four of the white patients were bilateral myopic individuals, with an average spherical equivalent of −2.87 for these

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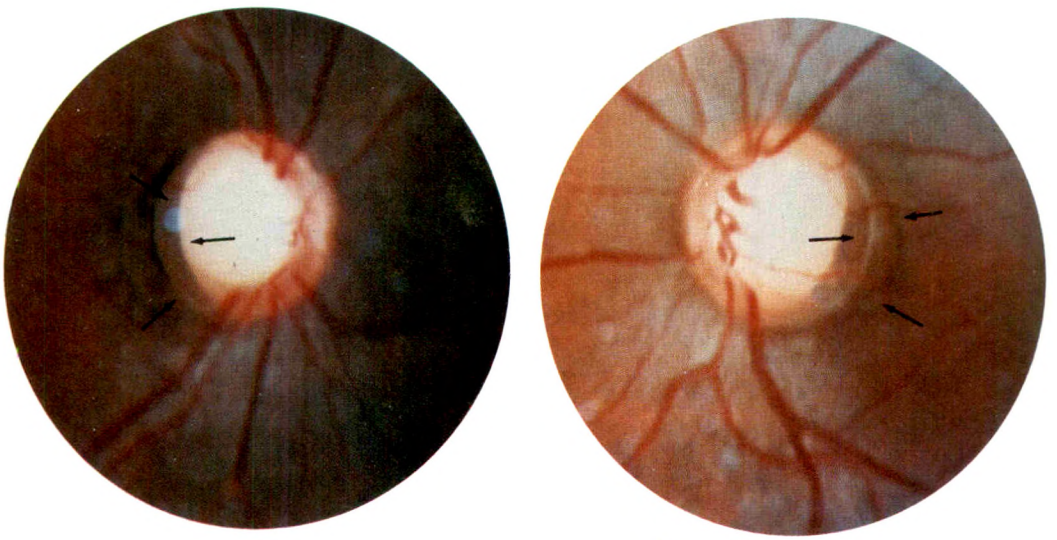

Fig. 1 (Shields). Case 1. Gray crescents in the optic nerve heads (arrows) obscure the inferotemporal portions of the neural rims.

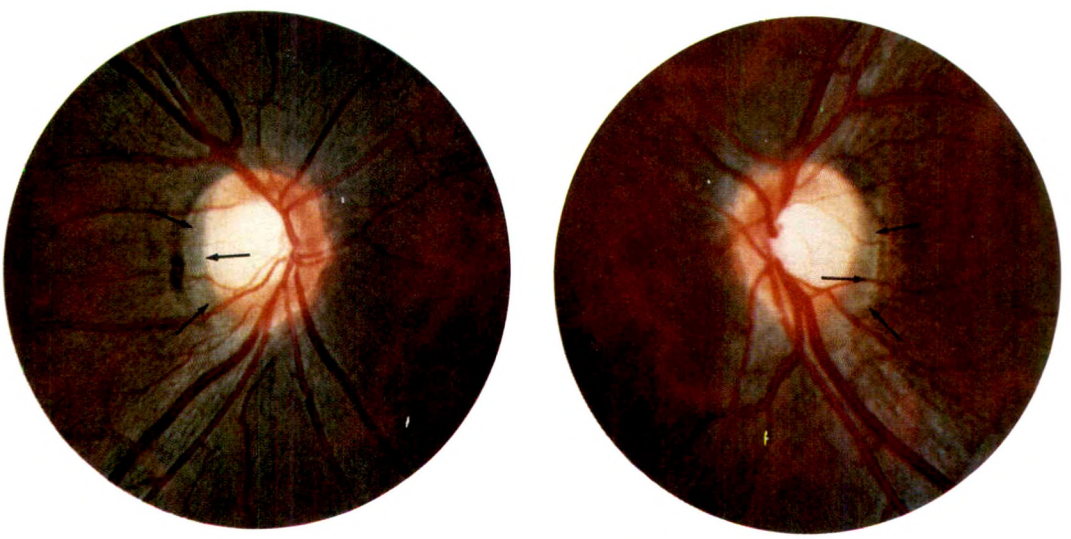

Fig. 3 (Shields). Case 18. Prominent gray crescents (arrows) in the optic nerve heads inferotemporally, with large physiologic cups extending to the inner margins of the crescents.

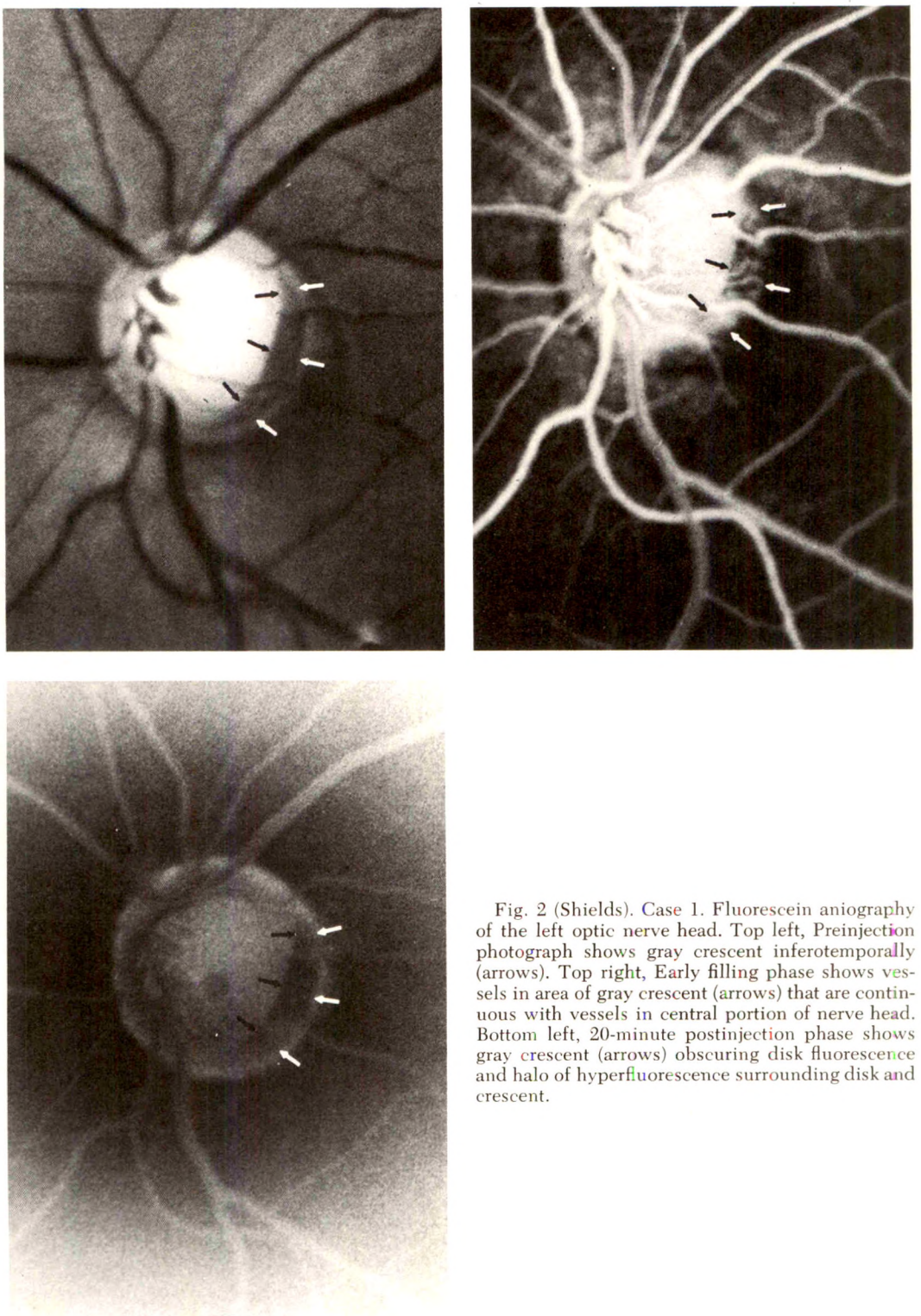

Fig. 2 (Shields). Case 1. Fluorescein aniography of the left optic nerve head. Top left, Preinjection photograph shows gray crescent inferotemporally (arrows). Top right, Early filling phase shows vessels in area of gray crescent (arrows) that are continuous with vessels in central portion of nerve head. Bottom left, 20-minute postinjection phase shows gray crescent (arrows) obscuring disk fluorescence and halo of hyperfluorescence surrounding disk and crescent.

TABLE

DATA OF PATIENTS WITH GRAY CRESCENTS IN THE OPTIC NERVE HEAD*

Case No., Age (yrs), Race, Sex	Refractive Error (spherical equivalent)		Intraocular Pressure (mm Hg)		Description of Optic Nerve Head					
					Cup Size (horizontal cup:disk)		Location of Gray Crescents		Peripapillary Pigment	
	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
1, 47, B, M	−0.50	+0.25	32	31	0.8	0.8	I	I	Yes	Yes
2, 19, W, F	−4.75	−4.75	18	18	0.2	0.2	S	I	No	No
3, 34, B, F	Plano	Plano	15	15	0.3	0.3	T	T	Yes	No
4, 49, B, F	+1.00	+1.00	14	14	0.6	0.6	T	T	Yes	Yes
5, 49, B, F	Plano	Plano	17	17	0.4	0.4	S	T	No	Yes
6, 69, B, F	+2.25	+2.25	19	19	0.8	0.8	I	I	Yes	Yes
7, 55, B, F	Plano	Plano	24	24	0.3	0.3	None	I	Yes	Yes
8, 42, B, F	Plano	Plano	13	14	0.8	0.8	I	I	Yes	Yes
9, 19, W, F	−4.00	−5.00	17	17	0.2	0.2	I	None	Yes	Yes
10, 10, B, M	+0.50	+0.50	14	14	0.8	0.8	T	I	Yes	Yes
11, 62, B, F	−3.00	−2.00	25	25	0.8	0.8	I	I	Yes	Yes
12, 40, B, M	+0.75	−0.50	20	22	0.8	0.8	T	T	Yes	Yes
13, 19, B, F	−1.50	−1.75	20	20	0.2	0.2	T	T	Yes	Yes
14, 52, B, M	+2.00	Plano	17	18	0.7	0.7	I	T	No	Yes
15, 34, B, M	+1.50	+1.50	18	17	0.2	0.2	T	T	Yes	Yes
16, 14, B, F	Plano	Plano	14	14	0.8	0.8	I	I	No	No
17, 36, B, F	−0.25	−0.50	23	24	0.7	0.7	T	T	Yes	Yes
18, 25, B, M	−3.50	−3.25	22	20	0.6	0.6	I	I	Yes	No
19, 34, B, F	−0.75	−0.75	24	19	0.7	0.7	T	I	Yes	Yes
20, 15, B, M	−2.25	−2.50	20	20	0.5	0.5	T	T	Yes	Yes
21, 56, B, M	Plano	+0.25	16	17	0.85	0.85	I	I	Yes	Yes
22, 28, B, F	−3.25	−5.25	15	15	0.4	0.4	T	None	Yes	Yes
23, 33, W, M	−1.00	−1.25	16	16	0.3	0.3	S	T	No	No
24, 26, W, F	−1.00	−1.25	12	12	0.5	0.5	None	S	No	No
25, 18, B, M	−0.50	−2.00	18	18	0.7	0.8	None	T	No	No
26, 46, B, M	Plano	Plano	15	14	0.8	0.8	T	T	Yes	Yes
27, 19, B, F	−1.00	−0.50	22	22	0.7	0.7	T	S	Yes	Yes
28, 39, B, F	Plano	Plano	17	16	0.7	0.7	None	I	No	Yes
29, 56, B, M	NLP	−1.00	29	17	1.0	0.7	None	I	Yes	Yes

*B designates black; W, white; I, inferotemporally; S, superotemporally; and T, temporally.

eight eyes. Ten of the 58 eyes were hyperopic, with the spherical equivalents ranging from +0.25 to +1.50 and averaging +0.90. Seventeen eyes had no detectable refractive error, and one had no light perception as the result of total glaucomatous optic atrophy.

Intraocular pressure in the 58 eyes ranged from 12 to 32 mm Hg and averaged 17.75 mm Hg. Four of the patients were receiving glaucoma medication, and three others were being followed up for glaucoma because of increased intraocular pressure. Horizontal cup:disk ratios ranged from 0.2 to 1.0 in the 58 eyes, with an average of 0.59.

The gray crescent in the optic nerve head was present in both eyes in 22 patients, and was unilateral in the remaining seven patients. The clinical appearance in all cases was that of a slate gray crescent within the peripheral tissue of the optic nerve head (Fig. 3). The crescents were located temporally in 24 eyes, inferotemporally in 21, superotemporally in five, and inferiorly in one eye. In 39 of the 51 eyes with the gray crescent, a darker peripapillary pigmented crescent was present in the quadrant corresponding to that of the gray crescent. A peripapillary pigmented crescent was also present in three of the seven eyes with no gray crescent.

The gray crescent in the optic nerve head was thin in some eyes and prominent in others. When the cup of the optic nerve head was large, it frequently touched the inner margin of the gray crescent. In one eye (Case 26), the temporal margin of the cup extended beyond the gray crescent, so that a portion of the crescent lay within the cup. This eye was also unusual in that two finger-like projections of pigment extended from the crescent further into the cup.

The results of fluorescein angiography were similar in the five cases studied; superficial vessels of the optic nerve head extended over the gray crescent, while the deep fluorescence of the nerve head was obscured, to variable degrees, by the crescent. Although the appearance of the gray crescent was virtually the same in white and black patients, fluorescein angiography suggested the pigmentation was less dense in the white patients, because it obscured less of the underlying nerve head fluorescence.

Discussion

The gray crescent in the optic nerve head was more common in individuals with increased pigmentation. The 29 patients in this study were predominantly black, and an examination of 100 consecutive black patients suggested that the gray crescent was common in this race. The few white patients with the gray crescent had dark complexions and one had ocular melanosis. An increased tendency toward myopia in these 29 patients was especially marked in the white patients. The relationship of increased pigmentation of the optic nerve head to increased general pigmentation is not unexpected, although the relationship to myopia is less evident. The higher than normal average intraocular pressures and horizontal cup:disk ratios in these patients indicate that many of the 29 patients had been referred for evaluation of possible glaucoma.

Although histologic studies are needed to confirm the exact location and nature of the gray crescent, the clinical and fluorescein angiographic findings in our study provide strong evidence that the crescent lies within the margins of the optic nerve head. Otherwise, the cup would have to be interpreted as extending to the disk margin in several cases, yet corresponding visual field loss was not seen in any of these eyes. Additionally, the gray crescent extended into the temporal periphery of the cup in one case. The fluorescein angiographic observation that the gray

crescents did not obscure superficial vasculature of the disk but did obscure, to variable degrees, the deep fluorescence of the nerve head, suggests that the pigmentation is near the region of the lamina cribrosa. The higher frequency among blacks suggests that this pigment may be an accumulation of melanocytes.

The main clinical importance of the gray crescent in the optic nerve head is the confusion it may create in interpreting disk cupping. As a glaucomatous cup enlarges, it most often extends first toward the inferotemporal or superotemporal disk margin.[2] This results in an uneven rim of neural tissue caused by selective thinning in one or both of these areas. In contrast, the margins of a physiologic cup tend to run parallel to the margins of the nerve head so that, even with a large physiologic cup, there will be an even rim of neural tissue for 360 degrees.[3] If the gray crescent is misinterpreted as lying peripheral to the optic nerve head, it would lead to the impression that the neural rim is thinned or absent in that area, which might be misdiagnosed as glaucomatous cupping. The tendency for the gray crescents to occur in one of the temporal quadrants of the optic nerve head further compounds the problem, because these are the most common areas for early thinning of the neural rim caused by glaucoma.

Summary

Twenty-nine patients had a slate-gray crescent within the peripheral tissue of the optic nerve head. Twenty-five of the patients were black; an examination of 100 consecutive black patients revealed the gray crescent in 12 cases. The gray crescents were usually bilateral and were most often located along the temporal or inferotemporal disk margin. Failure to recognize the anatomic location of the gray crescent may lead to misdiagnosis of disk cupping.

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THE EFFECT OF AQUEOUS HUMOR ON THE GROWTH OF SUBCONJUNCTIVAL FIBROBLASTS IN TISSUE CULTURE AND ITS IMPLICATIONS FOR GLAUCOMA SURGERY

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Filtering operations are generally effective for control of intraocular pressure in uncomplicated, medically unresponsive, open-angle glaucoma patients. However, in young patients with open-angle glaucoma, and in older patients with many types of secondary glaucoma, there is a much lower incidence of successful results with filtering procedures.[1,2] Furthermore, a second filtering procedure in an eye that has previously had unsuccessful glaucoma surgery is less likely to be successful than a primary filtering procedure.[3] The reason for extremely poor results obtained with filtering operations in aphakic individuals of all ages, who have no other complications, is not yet understood.[4]

Although filtering procedures are the preferred operations for open-angle glaucoma, there is little information to explain why failure of filtering occurs in certain individuals or under certain conditions. Little is known of the mechanisms for establishment or the maintenance of a filtering bleb. The histologic appearance of successfully functioning filtering blebs led Teng and associates[5] to conclude that aqueous humor has a degenerative effect on the collagen of sclera and Tenon's capsule. The presence of an inhibitory factor in the aqueous humor, which impedes the growth of tissue, has been hypothesized.[6] In animal studies, 100% concentrations of aqueous humor of both cows and rabbits did not support the growth of fibroblasts in tissue culture.[7,8] In lower concentrations the interaction between aqueous humor and fibroblasts was less predictable. To the best of our knowledge, no primate experiments, designed to study an inhibitory factor present in primate aqueous humor, have been done.

If an inhibitory property of aqueous humor exists in man, it might explain why filtering blebs can, in most patients, be formed. This factor might be altered, diminished, or lacking in certain individuals or disease states, and thus account for surgical failures in certain glaucoma patients.

We describe an in vitro tissue culture system, using human aqueous humor and homologous subconjunctival fibroblasts as an assay of aqueous humor inhibition, and a correlation between the results of this assay and the subsequent response to glaucoma surgery in a group of patients.

SUBJECTS AND METHODS

The patient population studied consisted of a series of randomly selected patients with senile cataracts or varying types of glaucoma. Informed consent was obtained from all patients. All cataract patients were free from other signs of intraocular disease. The glaucoma patients were a mixed group with primary or secondary glaucoma. Of the 45 patients studied, 22 had chronic open-angle glau-

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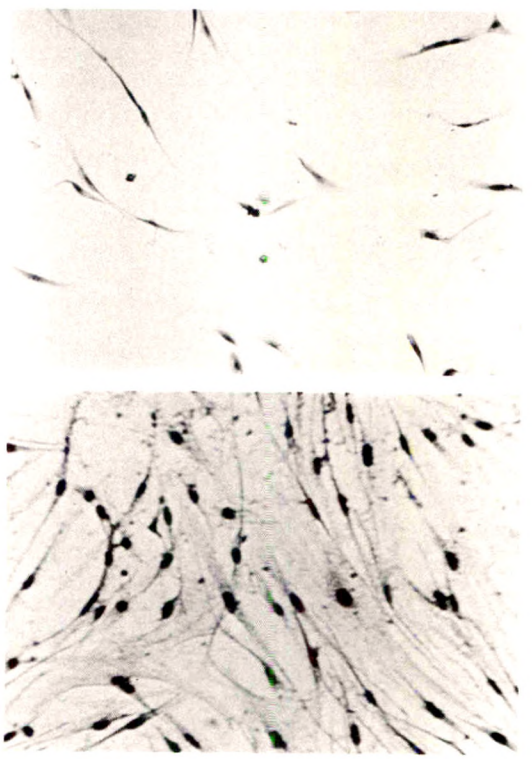
coma, nine had neovascular glaucoma, nine had aphakic glaucoma, one had uveitic glaucoma, and four had angle-closure glaucoma. The type of filtering procedure performed was primarily trabeculectomy (38), but five posterior lip sclerectomies and two Scheie procedures were included. All of the filtering operations were performed by the same surgeon.

At the time of surgery, before other surgical maneuvers, approximately 100 μl of aqueous humor was obtained by a paracentesis through clear peripheral cornea by using a 1 ml tuberculin syringe and a 25- or 27-gauge needle. A biopsy of subtenon's connective tissue was routinely performed at the same time. The tissue was placed in a sterile tube containing culture medium (CMRL-1415)[9] without sodium bicarbonate but containing antibiotics (100 units/ml penicillin, 100 mg/ml streptomycin, 2 μg/ml amphotericin B [Fungizone]). The tissue and aqueous humor were stored at 4°C and tissue explant cultures were initiated within 24 hours after collection of the samples. The tissue was rinsed in phosphate-buffered saline and cut into 1-mm^3 pieces with scalpels. Single pieces of tissue were placed into wells of a sterile microtest plate. The wells contained 50 μl of CMRL-1415 with sodium bicarbonate (1.9 mg/ml) (to counteract effects of CO_2 atmosphere) and 30% fetal calf serum or 50 μl of the patient's aqueous humor. When possible, a piece of tissue from an unrelated individual was cultured with the aqueous humor. After seven days in 5% CO_2, 95% air humidified at 37°C, the medium or aqueous humor was changed. After an additional seven days of incubation, the experiment was terminated. Phase microscopy was used to determine whether or not cellular outgrowth had occurred from the tissue explant during the 14 days of incubation. All grading of tissue culture growth was done in a masked fashion with the observer being unaware of the source of the sampling. In those microcultures where cell outgrowth was absent, the tissue explant was removed and placed in a tissue culture flask containing CMRL-1415 with 30% fetal calf serum to determine whether cellular outgrowth would occur on further incubation without aqueous humor. The microtest plates were then stained with Giemsa stain (5%) and cells, if present, were photographed (Figure).

Similar studies were done by using monolayer cultures initiated from human cadaver skin and from human subtenon's tissue. Tissue was prepared for explant cultures as described above and then placed in tissue culture flasks containing



(Figure) (Herschler, Claflin, and Fiorentino). Photomicrograph of cells grown in tissue culture. Top, Conjunctival fibroblasts grown in 100% aqueous humor from patient with aphakic glaucoma. Bottom, Conjunctival fibroblasts from same patient showing growth in CMRL-1415 with 30% fetal calf serum.

CMRL-1415 with 30% fetal calf serum. The cells were allowed to grow until confluent, at which time the pieces of tissue were removed and the cell monolayer was treated with 0.25% trypsin, 0.02% EDTA for ten minutes at 37°C. The cells were resuspended by gentle shaking, poured into a centrifuge tube, and centrifuged for ten minutes at 1,000 rpm (200 × g). The cells were resuspended, counted, and diluted so that 50 μl containing 3 × 10^3 viable cells were pipetted into wells of a microtest plate. CMRL-1415 or dilutions of aqueous humor ranging from 10 to 100% were added to the wells.

Results

The studies using monolayer cultures of skin or subtenon's fibroblast showed no inhibitory activity in human aqueous humor at any concentration. One-hundred percent aqueous humor obtained at the time of routine cataract extraction, however, inhibited the patient's own subtenon's tissue. No cellular outgrowth from the explant occurred in any of the 19 patients studied (Table 1). After 14 days' incubation in homologous aqueous humor, the explanted tissue, when placed in tissue culture medium, showed cellular outgrowth in six of the 19 samples obtained from cataract patients (showing viability of tissue after 14 days in aqueous humor) (Table 2).

Additionally, eight samples of aqueous humor (that inhibited a patient's own cellular outgrowth from the explant) were tested against unrelated subtenon's tissue. Three of the eight samples so tested supported cellular outgrowth from the unrelated tissue explant. Furthermore, five of six of these tissue explants were viable on transfer to CMRL-1415 with 30% fetal calf serum after 14 days in aqueous humor.

TABLE 1

FIBROBLAST GROWTH IN 100% AQUEOUS HUMOR*

	Cataract Patients	Glaucoma Patients
Growth	0	16
No growth	19	29

*$P < .01$; and corrected $\chi^2 = 7.21$.

TABLE 2

VIABILITY AFTER 14 DAYS IN 100% AQUEOUS HUMOR*

	Cataract Patients	Glaucoma Patients
Viable	6	37
Nonviable	13	7

*$P < .001$; and corrected $\chi^2 = 14.55$.

Forty-five patients (with either primary or secondary medically uncontrolled glaucoma) had aqueous humor sampled at the time of filtering surgery. In 29 of the 45 cases, cellular outgrowth did not occur in the presence of 100% aqueous humor (it behaved in a similar manner to cataract control population). Of these 45 patients, 16 had aqueous humor that did support the growth of their own fibroblasts. This result is significantly different from that obtained in the cataract control group ($P < .01$) (Table 1). After incubation in aqueous humor for 14 days, 37 of 44 (one was not tested) tissue explants grew (were viable) when transferred to CMRL-1415 with 30% fetal calf serum. This result also differs from that obtained with the cataract patients ($P < .001$) (Table 2).

The response to glaucoma surgery was evaluated in these same 45 patients. Their performance was graded on a scale from 1 to 3 to indicate response to glaucoma surgery. The patients graded 1 had control of intraocular pressure, a filtering bleb, and required no medication. Grade 2 was assigned to those patients who had blebs but required medication for satisfactory control. Patients graded 3 had surgical failures, without blebs, and with poor control of pressure. The graded responses to surgery were compared to the

TABLE 3

GROWTH IN AQUEOUS HUMOR AND SURGICAL RESULT*

	Group 1	Group 2	Group 3
Growth	2	2	12
No growth	15	7	7

*P < .01; Wilcoxon two sample rank test, Z-value = 2.99.

ability of the patient's aqueous humor to inhibit fibroblast outgrowth from the homologous tissue explant (Table 3). A positive relationship between surgical result and inhibitory activity was evident (P < .01). We also compared the surgical results with tissue viability as tested by transferring the explant to medium after 14 days' incubation in homologous aqueous humor (Table 4). A significant relationship was also established (P < .01).

DISCUSSION

Our study confirms in the laboratory what previous investigators[5,6] have speculated from animal experiments and clinical observations in human patients, that human aqueous humor does have inhibitory properties and is able to inhibit the outgrowth of subconjunctival fibroblasts from explants in tissue culture. Aqueous humor removed from patients with senile cataracts but no other known ocular disease consistently inhibited cell outgrowth of conjunctival fibroblasts from explants. Moreover, the effect was such that two thirds of the tissue explants were no longer able to exhibit cellular outgrowth in stimulated medium after 14 days of incubation in aqueous humor. However, this inhibition involves only an effect upon initiation of cellular outgrowth from tissue explants because cell monolayers continue to grow in culture and are not inhibited by aqueous humor.

TABLE 4

VIABILITY AND SURGICAL RESULT*

	Group 1	Group 2	Group 3
Viable	11	7	19
Nonviable	6	1	0

*P < .01; Wilcoxon two sample rank test, Z-value = 2.63.

It is difficult to distinguish between a tissue inhibition and a lack of sufficient nutrient material when explaining the lack of fibroblast growth in tissue culture. The addition of tissue culture medium to aqueous humor, even in relatively low concentrations, allows cellular outgrowth from the explant. This observation would thus seem to support the hypothesis that a lack of nutrient material is important to the absence of tissue culture growth with aqueous humor medium. In contrast, the experiment using 100% aqueous humor with known inhibitory activity and unrelated subconjunctival explants that resulted in growth of some specimens, as well as the observed growth of skin fibroblasts or pre-established subconjunctival fibroblast monolayers in aqueous humor media, are consistent with the hypothesis that the lack of cellular outgrowth of the patient's own fibroblasts in homologous aqueous humor is the result of a weak and easily overcome inhibition, and that this inhibition may require an element of self-recognition (be more effective against one's own tissue).

The aqueous humor of patients with varying types of glaucoma often lacked the inhibitory properties found in aqueous from cataract patients (P < .01). This was an unexpected finding, and raises the possibility that a primary defect in aqueous humor biology may be an important factor in the development of high intraocular pressure in open-angle glaucoma. Most speculation in the past as to the abnormality in open-angle glaucoma has focused on the outflow system itself, thus overlooking the possibility of a primary aqueous humor defect. The possibility

does exist that basic differences in preoperative medications between cataract patients (mydriatic-cycloplegic) and glaucoma patients (miotics, epinephrine, carbonic anhydrase inhibitors) account for some of the observed differences in tissue culture inhibition. Unfortunately, because of ethical and technical considerations, miotics cannot be prescribed for cataract patients preoperatively nor can cycloplegics be prescribed for glaucoma patients.

Previously published reports of the rate of success of formation of filtering blebs and control of intraocular pressure are similar for all types of filtering operations (trephine, punch, Scheie, iridencleisis, and trabeculectomy).[10] Complications vary with the modifications of filtering procedures, but almost all series limited to primary open-angle glaucoma report control of pressure in 80 to 90% of all cases.[11] Surgical technique may be only one factor (and perhaps minor) in determining surgical results. In our series, the outcome of the filtering procedures in the glaucoma patients studied was significantly related ($P < .01$) to the tissue culture data for each patient. The basic biology of the patient seems to be an important variable.

Although the correlation between surgical success and tissue culture activity was significant, it was not perfect (that is, a few patients whose aqueous humor supported fibroblast proliferation did maintain filtering blebs and some whose aqueous humor did not support proliferation did not maintain blebs). The aqueous humor sampled in the study was primary in nature, undisturbed by surgery. It is the secondary aqueous humor that is probably of greater significance for the outcome of the filtering bleb. Improvement in the rate of success with filtering operations may rest more with our ability to manipulate in vivo the nature of aqueous humor physiology upon proliferation of tissue fibroblasts, rather than with further alterations in the type of surgery.

Summary

We used aqueous humor from cataract patients and glaucoma patients as a medium for tissue culture of subconjunctival fibroblasts. The aqueous humor from cataract patients consistently inhibited the growth of their own subconjunctival fibroblasts, whereas that of some of the glaucoma patients did not. We found a significant correlation between the success of the filtering operation and the ability of that patient's aqueous humor to inhibit the growth of fibroblasts in tissue culture.

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AQUEOUS HUMOR CHANGES AFTER EXPERIMENTAL FILTERING SURGERY

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Evidence suggests that aqueous humor may have an inhibitory effect on the growth of various tissues. Lack of healing of surgical iris lesions in rabbit[1] or man[2,3] has been noted. Similarly, poor viability of sclera implanted in the anterior chamber suggests that aqueous humor may retard growth of transplanted tissue.[4] In tissue cultures of chick embryo or heart fibroblast material, growth is inhibited when aqueous humor is provided as nutrient material.[5] Conversely, many elements of excised iris do proliferate in nonaqueous humor tissue culture media.[6]

Recent studies in humans show that aqueous humor sampled at the time of cataract surgery consistently fails to support growth of subconjunctival biopsy material in tissue culture.[7] In the same study, a proportion of aqueous humor samples from glaucomatous eyes did support growth of homologous subconjunctival fibroblasts. In these eyes the growth of subconjunctival fibroblasts cultured in aqueous humor was correlated with the failure of filtering surgery.

This tissue culture assay, however, did not completely differentiate that group of eyes which showed a successful surgical result from those that failed. The variability in this assay may reflect the greater importance of postoperative secondary aqueous humor with respect to the ultimate success of filtering surgery in glaucomatous eyes. Because secondary aqueous humor from surgical glaucoma patients is not routinely available, we undertook the present study to establish an experimental model that would facilitate the study of secondary aqueous humor in primate eyes.

MATERIAL AND METHODS

Seventeen eyes from four rhesus and 13 owl monkeys were subjected to conventional filtering surgery. After intramuscular injection of 0.05 ml of phencyclidine HCl (Sernylan) and intraperitoneal injection of 0.1 ml of sodium pentobarbital (Nembutal), aqueous humor was aspirated from the anterior chamber through a 30-gauge needle into a 1-ml plastic syringe. Thermal sclerostomy was then performed superiorly on the globe in the standard manner.[8] A 3 × 2-mm segment of Tenon's tissue was excised and placed in tissue culture medium (CMRL-1415). The conjunctiva was closed in a routine manner.

At two days, and again at one, two, four, and eight weeks after this surgery, monkeys were re-anesthetized with 0.05 ml of phencyclidine HCl. At each interval, intraocular pressure was recorded by using pneumatic applanation tonometry. Aqueous humor (0.2 ml) was aspirated from the anterior chamber of the operated eye and subconjunctival tissue was excised inferotemporally.

In nine owl and four rhesus monkey eyes, simple aspiration of aqueous humor

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from the contralateral unoperated eye was substituted for the more complete operative procedure. These eyes were reexamined at two, seven, and 14 days after aspiration.

Subconjunctival biopsy material was placed immediately in carrier medium, (CMRL-1415 without bicarbonate), and refrigerated along with aqueous humor samples. Biopsy specimens were divided into equal parts and then cultured in either 100% aqueous humor or CMRL-1415 with 30% fetal calf serum. Culture techniques used were those previously described.[7] After two weeks each tissue culture was assayed for presence of cellular proliferation.[7] The tissue testing in CMRL-1415 with 30% fetal calf serum was performed to establish the viability of a given explant.

In the 17 operated eyes, as well as the 13 eyes undergoing paracentesis, tissue samples were cultured in aqueous humor from the same eye. Aqueous humor from eight of the preparacentesis eyes was used as culture media for subconjunctival tissue from the contralateral unoperated eye. In 11 of the experimental animals, aqueous humor from the contralateral unoperated eye was mixed with an equal volume of one-week postoperative aqueous humor from the operated eye and used as nutrient medium for biopsy material from the operated eye. In six eyes, this same preoperative aqueous humor was diluted by an equal volume of normal saline and used as the culture medium.

In four owl and three rhesus monkey eyes, biopsy material was cultured in aqueous humor aspirated preoperatively from the eyes of different animals. In an additional six owl and four rhesus monkey eyes, biopsy material from eyes of different animals was cultured in aqueous humor aspirates from operated eyes one week postoperatively.

Statistical analysis consisted of chi-square comparison of relative frequencies of positive and negative culture growth between two populations of aqueous humor samples. Groups of samples were compared to the characteristic growth patterns of cells cultured in either preoperative primary aqueous humor or CMRL-1415 with 30% fetal calf serum.

Results

Of the 102 subconjunctival biopsy specimens cultured in CMRL-1415, 80 (78% of the samples) grew readily in tissue culture (Tables 1 and 2). That 22 specimens did not grow in CMRL-1415 reflects the probability that a given biopsy specimen will not be viable even in nutrient medium. Of 17 subconjunctival biopsy specimens for which preoperative aqueous humor was used as nutrient medium, only three showed growth. This difference between distribution of positive and negative growth when comparing subconjunctival tissue cultured in preoperative aqueous humor with samples grown in CMRL-1415 was statistically significant ($P<.001$).

In contrast, subconjunctival tissue incubated in postoperative aqueous humor samples two days after surgery grew in 14 of 17 cases. This represents a complete reversal of the pattern of growth seen with preoperative aqueous humor ($P< .001$). The proportion of positive cultures of fibroblasts grown in aqueous humor was indistinguishable from that seen when CMRL-1415 was used as culture medium ($\chi^2 = 0.056$). Aqueous humor sampled at one, two, and four weeks also supported growth of subconjunctival fibroblasts in tissue culture. Of six eyes tested two months after surgery, only two aqueous humor samples supported tissue culture growth. This distribution of positive cultures could not be distinguished from that seen with tissue samples cultured in preoperative aqueous humor.

At seven days after glaucoma surgery,

TABLE 1

FIBROBLAST GROWTH IN TISSUE CULTURE IN EYES ASSAYED AT VARIOUS INTERVALS AFTER FILTRATION SURGERY*

Eye	Time After Surgery†					
	0 Days	2 Days	1 Week	2 Weeks	4 Weeks	8 Weeks
Owl monkey						
433 RE	−(+)	+(+)	+(+)	+(+)	−(+)	+(+)
377 RE	−(+)	−(+)	−(+)	+(+)	−(+)	−(+)
302 LE	−(−)	−(−)	+(+)	+(+)	+(+)	−(+)
377 LE	−(+)	+(+)	+(+)	+(+)	+(+)	−(+)
434 LE	−(−)	+(+)	+(+)	+(+)	+(+)	+(+)
511 RE	−(−)	+(+)	/	+(+)	+(+)	−(+)
512 RE	+(+)	+(+)	/	/	+(+)	/
513 RE	+(+)	+(+)	/	/	+(+)	/
514 RE	−(+)	+(+)	/	/	/	/
538 RE	−(−)	+(+)	+(−)	/	/	/
539 RE	−(−)	+(−)	+(+)	/	/	/
540 RE	−(−)	−(−)	+(+)	/	/	/
541 RE	−(−)	+(−)	+(+)	/	/	/
Rhesus monkey						
544 RE	+(+)	+(+)	+(+)	+(+)	/	/
545 RE	−(+)	+(+)	+(+)	+(+)	/	/
546 RE	−(+)	+(+)	+(+)	+(−)	/	/
547 RE	−(+)	+(+)	+(+)	−(+)	/	/
Positive cultures, %	18	82‡	92‡	90‡	75‡	33

*Results from fibroblast tissue culture assay of specimens grown in CMRL-1415 (viability test) or in parentheses adjacent to results of assay for tissue specimens (from the same eye) grown in 100% aqueous. Control specimen indicates viability of tissue specimen in nutrient medium.

†−designates no growth of tissue specimen in test solution (either 100% aqueous or CMRL-1415); +, growth of tissue specimen in test solution (either 100% aqueous or CMRL-1415); and /, assay not performed at this time interval.

‡Percentage of positive cultures of fibroblasts grown in aqueous samples differed significantly from that seen in normal preoperative samples (χ^2, $P < .001$).

aqueous humor samples from the operated eye were used as a medium for subconjunctival tissue removed from the eight unoperated contralateral eyes. All specimens showed growth in tissue culture. In a separate study, preoperative aqueous humor from the contralateral unoperated eyes was mixed with an equal volume of postoperative aqueous humor from 11 operated eyes. In all instances, the aqueous humor mixture supported growth of fibroblasts in tissue culture. This finding is in contrast to that seen when preoperative aqueous humor from six animals was mixed with equal concentrations of normal saline. In five of six cases the mixture failed to support growth of fibroblasts. In an additional seven eyes subconjunctival biopsy specimens from one monkey were incubated with preoperative aqueous humor from another monkey. In no case did growth of fibroblasts occur. Finally, in another ten eyes, subconjunctival biopsy tissue from one monkey was cultured in postoperative aqueous humor from another monkey. In all instances, growth of fibroblasts occurred.

To investigate whether aspiration itself was sufficient to alter aqueous humor physiology, 0.2 ml of aqueous humor was removed from the contralateral unoperated eyes of 13 of the original 17 monkeys. In only two of the 13 cases did this aqueous humor sample support fibroblast

TABLE 2

FIBROBLAST GROWTH IN TISSUE CULTURE IN EYES STUDIED AFTER ANTERIOR CHAMBER ASPIRATION*

Eye	Time After Anterior Chamber Aspiration†		
	0 Days	2 Days	7 Days
Owl monkey			
303 LE	−(−)	+(+)	−(−)
511 LE	/	+(+)	+(+)
512 LE	/	+(+)	+(+)
513 LE	/	+(+)	+(+)
514 LE	/	+(+)	+(+)
538 LE	+(+)	+(−)	+(+)
539 LE	−(−)	−(+)	−(−)
540 LE	−(−)	−(+)	−(+)
541 LE	−(−)	−(+)	+(+)
Rhesus monkey			
544 LE	+(+)	+(+)	/
545 LE	−(+)	+(−)	/
546 LE	−(−)	−(+)	/
547 LE	−(+)	+(+)	/
Positive cultures, %	22	69‡	67‡

*Results from fibroblast tissue culture assay of specimens grown in CMRL-1415 (viability test) or in parentheses adjacent to results of assay for tissue specimens (from the same eye) grown in 100% aqueous. Control specimen indicates viability of tissue specimen in nutrient medium.

†− designates no growth of tissue specimen in test solution (either 100% aqueous or CMRL-1415); +, growth of tissue specimen in test solution (either 100% aqueous or CMRL-1415); and /, assay not performed at this time interval.

‡Percentage of positive cultures of fibroblasts grown in aqueous samples differed significantly from that seen in normal preoperative samples (χ^2, $P < .05$).

growth (Table 2). These samples from contralateral eyes behaved indistinguishably from the preoperative aqueous humor samples of the 17 fellow eyes assayed before glaucoma surgery (Table l, $\chi^2 = 0.023$). At two days, and again at one week after aspiration, aqueous humor samples taken from these same eyes supported fibroblast growth in 69 and 67% of cases, respectively (Table 2). Postparacentesis aqueous humor samples differed significantly from preparacentesis samples in their ability to support growth ($P < .05$).

DISCUSSION

In all but five of 26 experimental eyes, primary (preoperative) aqueous humor samples failed to support initiation of growth of fibroblast tissue cultures. That some aqueous humor samples did support proliferation of tissue culture fibroblasts may represent either individual variation from monkey to monkey or variability in the tissue culture assay.

Postoperatively, secondary aqueous humor samples routinely supported initiation of fibroblast growth in tissue culture. In monkey eyes, where secondary aqueous humor routinely supported initiation and continued growth in tissue culture, filtration surgery was routinely unsuccessful in establishing a bleb. This finding supports the hypothesis that characteristics of secondary aqueous humor (shown by tissue culture assay) may be particularly pertinent to the ultimate success of filtration surgery.[7]

What changes are occurring in these operated eyes remains unclear. The growth of tissue specimens taken from unoperated contralateral eyes cultured in secondary aqueous humor would indicate that altered aqueous humor physiology accounts for the tissue culture growth rather than alterations in subconjunctival tissues. Furthermore, results of tissue culture assays performed with primary aqueous humor from contralateral unoperated eyes indicate that this aqueous humor alteration is confined to the surgical eye.

The data from experiments involving human aqueous humor samples are most consistent with the hypothesis that a weak inhibitor of fibroblast growth is present in primary aqueous humor samples taken from eyes of preoperative cataract patients and some glaucomatous patients. In the present animal experiments, characteristic responses in tissue culture to both primary and secondary aqueous humor, mixed in equal portions, showed cell proliferation. Furthermore, these re-

sponses to aqueous humor samples did not appear to be either animal or even species specific.

These results are compatible with two hypotheses. One possibility is that materials added to secondary aqueous humor (perhaps after local breakdown in the normal blood-eye tissue barriers) are sufficient to support growth of fibroblasts. Alternatively, addition of certain substances to postoperative aqueous humor could mask or destroy a weak inhibitor normally present in primary aqueous humor. Either hypothesis is supported by the observation that mixtures of equal portions of preoperative and postoperative aqueous humor samples can initiate growth of biopsy material assayed in tissue culture.

Even with micro-assays of aqueous humor constituents, it is difficult to determine which hypothesis most accurately represents what changes are occurring in these operated eyes. Some combination of these several possibilities may best explain the experimental findings. Alternative theories not withstanding, this aqueous humor assay may be of significance, because the present animal model allows the opportunity to study and possibly change the effects of surgery on aqueous humor physiology.

Summary

We studied aqueous humor of rhesus and owl monkeys for its effect on the growth of subconjunctival fibroblasts in tissue culture. Aqueous humor samples obtained before glaucoma surgery inhibited the initiation of growth of fibroblasts. However, postoperative aqueous humor samples supported growth of fibroblasts. The change in aqueous humor physiology lasted for up to two months after glaucoma surgery. Our study indicated that possibly material added to the postoperative aqueous humor inactivates an inhibitor normally present in primary aqueous humor. An alternative explanation would be that primary aqueous humor, in contrast to secondary aqueous humor, lacks sufficient nutrient material to support fibroblast growth in tissue culture.

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PENETRATING KERATOPLASTY IN MOOREN'S ULCER

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A report by Wood and Kaufman[1] suggested that there are two different types of Mooren's ulcer: (1) a limited, unilateral type that is amenable to surgical therapy, and (2) a relentlessly progressive, bilateral type that results in total corneal stromal destruction, which is unresponsive to medical or surgical therapy. The second type usually results in a thin, vascularized cornea that is totally opacified and covered with conjunctival epithelium. In these end-stage corneas, the ulcerative process resolves.[2]

We describe the technique and results of corneal transplantation in three eyes with opacified end-stage corneas resulting from Mooren's ulcers.

CASE REPORTS

Case 1—A 73-year-old woman developed herpes zoster in the distribution of the ophthalmic division of the fifth cranial nerve on the left side in June 1973. This was complicated by an anterior uveitis in her left eye. During the following six months, painful peripheral corneal ulcers developed in both eyes that progressed circumferentially and then centrally despite treatment with systemic and topical corticosteroids, cycloplegics, antibiotics, soft contact lenses, repeated conjunctival excisions, cryotherapy, and a doughnut-shaped lamellar graft in the right eye. High intraocular pressures in both eyes were reduced to 25 mm Hg by treatment with 250 mg of acetazolamide every six hours and epinephrine bitartrate 2% twice daily. By 1976 both corneas were totally destroyed by the disease process, leaving only some residual posterior corneal stroma covered by vascularized conjunctival epithelium. The conjunctival hyperemia gradually disappeared (Figs. 1 and 2). Her visual acuity at that time was light projection in both eyes. That same year she underwent an intracapsular cataract extraction in her right eye in an attempt to obtain some functional vision. Postoperatively, the cornea opacified even further, but visual acuity remained at light projection. After the disease had been quiescent for approximately ten months, a 7.5-mm penetrating keratoplasty was performed on the right eye in July 1976. After the host cornea was removed, a limited vitrectomy was performed, and a donor cornea with intact donor epithelium was sutured in place with 16 interrupted

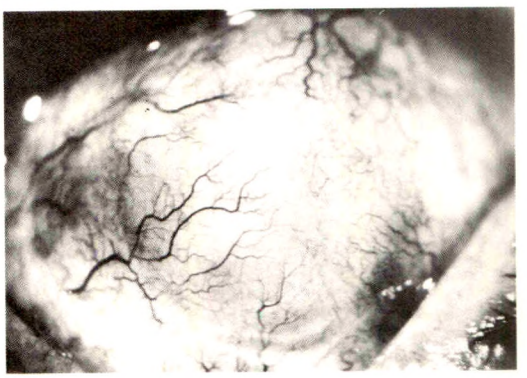

Fig. 2 (Brown and Mondino). Case 1. Preoperative appearance of left eye.

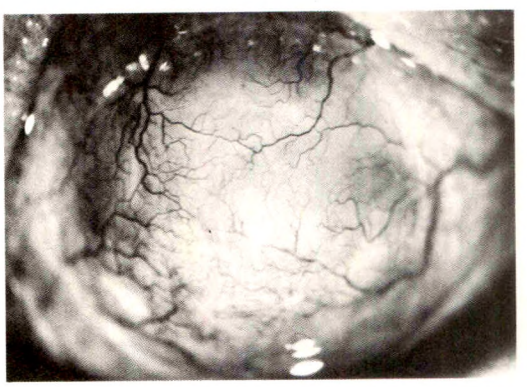

Fig. 1 (Brown and Mondino). Case 1. Preoperative appearance of right cornea in 73-year-old patient with bilateral, end-stage Mooren's ulcers.

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9-0 black silk sutures. The sutures were extended into the sclera because the thin peripheral cornea left little tissue to which the sutures could be anchored. Silk sutures were used to stimulate vascularization and thereby promote healing of the donor graft to the recipient tissue. Additionally, silk sutures are less elastic than nylon sutures so that there would be less likelihood for them to pull through the thin recipient tissue. Postoperatively, the corneal transplant remained transparent, and treatment consisted of prednisolone acetate 1% every two hours, 250 mg of acetazolamide every six hours, and echothiophate iodide (Phospholine Iodide) 0.25% twice daily. One month postoperatively, the surgeon began removing alternate interrupted sutures to decrease an inflammatory reaction stimulated by the exposed knots, and to prevent recurrence of Mooren's ulcer. As a result, the graft margin lifted slightly from its attachment to the host cornea from 12 to 3 o'clock. An epithelial erosion developed in this area that was attributed to inadequate wetting by the tear film because of the overriding at the donor-host junction. A continuously worn soft contact lens quickly healed the erosion, which left a superficial stromal opacity in this area. The best corrected visual acuity was 6/15 (20/50). Four months postoperatively, the intraocular pressure was increased to 35 mm Hg and remained at that level despite maximal medical therapy. Cyclocryotherapy was performed over the inferior 180 degrees of her globe. Thereafter, the intraocular pressure remained between 8 and 16 mm Hg, but the visual acuity decreased to 6/60 (20/200). An episode of graft rejection developed one year postoperatively that was reversed by topical and subconjunctival corticosteroids. Except for the opacity in the area of the epithelial erosion, the graft has remained transparent (Fig. 3) and the best corrected visual acuity is 6/60 (20/200).

In May 1978 a 7.5-mm penetrating corneal transplant, cataract extraction, and anterior vitrectomy were performed on the left eye. The same technique was used as in the right eye except that interrupted 10-0 Prolene sutures were used. Postoperatively, the graft has remained transparent (Fig. 4). The interrupted sutures were all removed by the third postoperative month. The intraocular pressure has remained within normal limits. The corrected visual acuity is 6/60 (20/200).

Case 2—A 46-year-old woman with diabetes developed painful, peripheral corneal ulcers in both eyes in 1975. Despite topical corticosteroids, soft contact lenses, and repeated conjunctival excisions, the ulcers progressively encircled both corneas. Under topical anesthetic the intact, but edematous, central corneal stroma in the right eye was excised with corneal scissors. The conjunctival epithelium immediately healed over the central cornea, and the right eye became free of pain and inflammation (Fig. 5). When visual acuity in the left eye had decreased to counting fingers, the central island of noninvolved corneal stroma was also excised and within two weeks the conjunctival epithelium healed over this cornea, which also became free of pain and inflammation.

In April 1977, four months after disease activity had subsided, a 7.5-mm penetrating corneal transplant was performed on the right eye by using the same technique as described in the first case, except that Prolene sutures were used and an intracapsular lens extraction was performed as well. Postoperatively, the corneal graft remained transparent (Fig. 6). The intraocular pressure remained within normal limits, and the sutures were gradually removed between the first and the fourth postoperative months. The best corrected visual acuity has remained at 6/7.5 (20/25).

Discussion

In Case 1, bilateral Mooren's ulcer destroyed all but the posterior corneal stro-

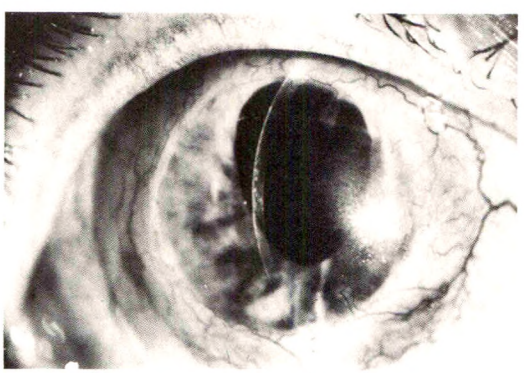

Fig. 3 (Brown and Mondino). Case 1. Appearance of right cornea 32 months after combined corneal transplant and cataract extraction.

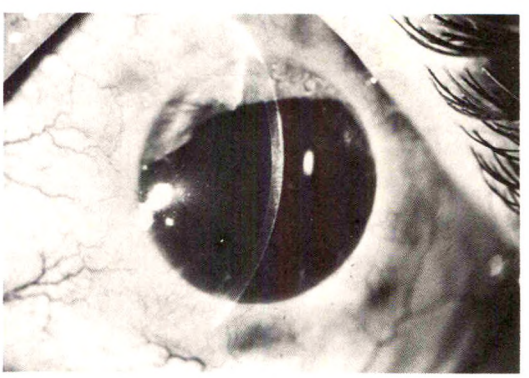

Fig. 4 (Brown and Mondino). Case 1. Appearance of left cornea one year after combined corneal transplant and cataract extraction.

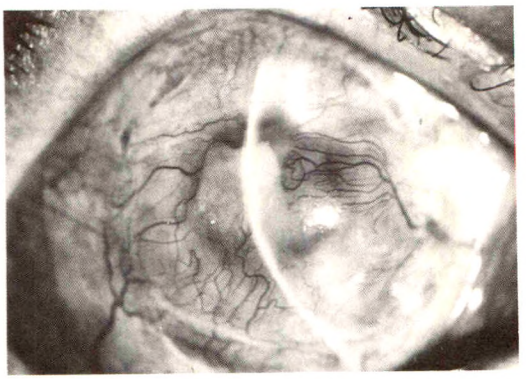

Fig. 5 (Brown and Mondino). Case 2. Right cornea of 46-year-old patient with bilateral end-stage Mooren's ulcers.

ma that was covered by vascularized conjunctival epithelium in both eyes. In Case 2, inflammatory disease activity was interrupted by excising the remaining noninvolved central corneal stroma in each eye. This approach was recommended by Maumenee (unpublished data, 1972), who suggested that this treatment accelerates healing in Mooren's ulcer. The technique in the present study differed from routine corneal grafting only in the use of interrupted silk sutures that were anchored in scleral tissue so that they would not pull through the thin host cornea, which consisted of Descemet's membrane covered by conjunctival overgrowth.

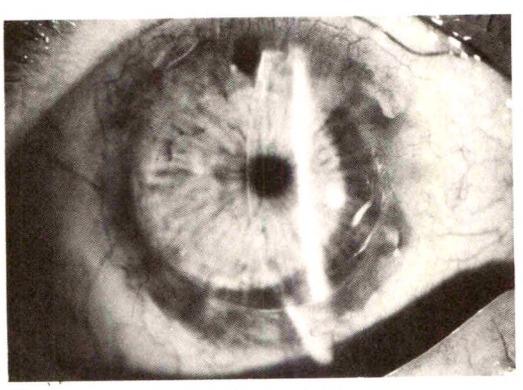

Fig. 6 (Brown and Mondino). Case 2. Appearance of right cornea two years after combined corneal transplant and cataract extraction.

Several reports have described the use of lamellar or penetrating keratoplasty in patients with active Mooren's ulcer.[1–6] Although an occasional success has been reported, the results are generally poor, especially in bilateral simultaneous cases, and often are complicated by extension of the disease process into the donor tissue with resultant necrosis and sloughing.

The postoperative course in our two patients was not uneventful. However, there was no recurrence of Mooren's ulcer. The successful penetrating corneal grafts were attempted only after all but the posterior corneal stroma had been either destroyed by the disease process or surgically excised. Additionally, the grafts were not performed in a setting of acute disease activity but only after the conjunctival epithelium covered the cornea with a quiescent period of at least four months. The lack of recurrent ulcerations in these eyes may relate to the finding in a small number of patients that healing after complete corneal destruction was associated with a loss of cellular immunity to soluble corneal antigen in patients with Mooren's ulcer.[7]

Summary

Two patients had bilateral, simultaneous Mooren's ulcers that progressed to almost total loss of the corneal stroma in all eyes. The conjunctival epithelium eventually healed over these thinned corneas and the eyes were free of pain and inflammation. Three of the four eyes had combined 7.5-mm penetrating corneal transplants and cataract extractions performed at least four months after disease activity had subsided. All transplants have remained transparent from one to three years postoperatively and there has been no evidence of recurrence of Mooren's ulcers.

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Ophthalmic miniature

Blind people are fond of geography, and they are assisted in the study by maps of ingenious construction. These maps are made of wood, the cities are pins of different shape, the rivers are like real river beds, and the mountains are ridges. The boundaries are well enough defined to be followed with the finger. Names are in raised or depressed letters either on the surface or on the back of the blocks. Sometimes these maps are so constructed that the various States of the Union, for example, may be taken apart. The exercise of putting together such a map gives a blind pupil a better idea of the size, shape, boundaries, and relative position of the States than is obtained by most children who have the use of their eyes.

The Illustrated American
August 30, 1890

VARICELLA DENDRITIC KERATITIS

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In 1973, Pavan-Langston and McCulley[1] studied three cases of dendritic keratitis associated with ophthalmic herpes zoster, and isolated varicella-zoster virus from the corneal lesion. In the same year, Piebenga and Laibson[2] described nine patients with ophthalmic herpes zoster who developed dendritic keratitis. The biomicroscopic characteristics distinct from herpes simplex dendritic keratitis were described by those investigators. Recently, differentiation between herpes simplex and zoster epithelial keratitis was further detailed by Marsh, Fraunfelder, and McGill.[3]

Varicella is caused by the same virus as herpes zoster; therefore, dendritic corneal lesions possibly may occur in patients with varicella. Although varicella is a common infectious disease in childhood, such a corneal involvement has been documented only in one case reported by Nesburn and associates.[4] We encountered two cases of varicella dendritic keratitis documented by immunofluorescence.

MATERIAL AND METHODS

Epithelial scrapings were taken from the corneal lesion by using the slit-lamp microscope and benoxinate anesthesia.

Convalescent serum was obtained from a patient with ophthalmic herpes zoster, three weeks after the onset of eruption. The complement-fixing antibody titers for varicella-zoster virus and herpes simplex virus were 1:1,024 and 1:4 respectively. Gamma-globulin was fractionated and conjugated with fluorescein isothiocyanate according to the method of Kawamura.[5] Human embryonic kidney cells infected with varicella-zoster virus showed a bright fluorescence, when stained with the conjugate. The staining titer (reciprocal of the highest dilution giving recognizable specific staining) was 1,000. A diluted working solution (50 times) showed no cross-reaction with other herpes group viruses and vaccinia virus.

The gamma-globulin fraction of antiherpes simplex serum was prepared from rabbits inoculated with type 1 herpes simplex virus, and conjugated with fluorescein isothiocyanate.

Specimens on a glass slide were fixed for ten minutes in acetone, air dried, and then covered with the conjugated globulin. After incubation for one hour in humidified air at 37°C, the slides were washed in phosphate-buffered saline and mounted with glycerin. Observation was carried out with a Nikon fluorescent microscope.

Part of the corneal specimen was inoculated into two tubes of human embryonic lung cell cultures maintained on minimum essential medium with 10% fetal bovine serum, kanamycin, streptomycin, and penicillin. The tubes were incubated at 37°C; the medium was changed every four days for three weeks. When no cytopathic effect appeared, these cells were scraped and transferred to fresh cell cultures.

CASE REPORTS

Case 1—A 7-year-old boy had a two years' history of vernal conjunctivitis. At the beginning of May 1976, he was febrile for two days, and then developed vesicular eruptions on the face and trunk. Two

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weeks before the onset of symptoms, he was exposed to a classmate who subsequently developed varicella. The diagnosis of varicella was made by his family physician. During the acute phase of the disease, no ocular changes were noted by the patient's mother. He was seen at an ophthalmologist's office on May 24, 1976, complaining of itchiness in both eyes. A minimal papillary reaction on the upper tarsal cojunctiva bilaterally was noted. The bulbar conjunctiva was not hyperemic. A small area of subepithelial haze was noted in the right cornea, above the pupillary zone. Topical 0.02% dexamethasone, twice a day, was prescribed.

Because the right cornea became cloudy, the patient was referred to our clinic on July 5, 1976. On examination, the central part of the right cornea had a disciform stromal haze and edema, about 6 mm in diameter, with epithelial bedewing and keratic precipitates. A mild pericorneal hyperemia and 2+ cells in the anterior chamber were observed. Visual acuity was R. E.: 6/30 (20/100) and L. E.: 6/5 (20/16). The diagnosis of herpes simplex disciform keratitis was tentatively made. Treatment was instituted with 0.5% atropine drops once a day, 0.1% betamethasone twice a day, and idoxuridine drops four times a day. As the stromal edema and iritis improved, the medications were tapered slowly. Visual acuity of the right eye improved to 6/7.5 (20/25) in the middle of August 1976.

On Aug. 30, 1976, disciform keratitis flared up, and the medications were increased to the previous dosages. One week later, a new epithelial lesion appeared in the upper temporal part of the right cornea. It was white-gray and stellate, slightly elevated, and stained poorly with fluorescein (Fig. 1). The appearance suggested varicella dendritic keratitis. Epithelial scrapings of the corneal lesion were subjected to the direct immunofluorescence. The result was positive for varicella-zoster virus, and negative for herpes simplex virus. Viral isolation was not done. The serum complement-fixing antibody titer was less than 1:4 for both varicella-zoster virus and herpes simplex virus. Topical corticosteroid medications were stopped, with continuation of atropine and idoxuridine. Re-epithelization of the scraped lesion was completed in three days. Two weeks later, the stromal haze and iritis grew worse, and 0.1% betamethasone three times a day, was resumed. The medications were tapered slowly over the ensuing four months' period, and were discontinued at the end of February 1977.

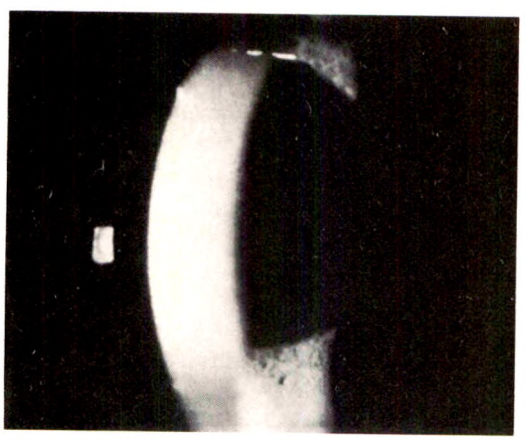

Fig. 1 (Uchida, Kaneko, and Hayashi). Case 1. Varicella epithelial stellate lesion and stromal disciform haze of right cornea.

During the next year, the disciform keratitis and iritis recurred three times, and corticosteroid and atropine drops were needed to suppress inflammation each time. The intraocular pressure remained normal. The central portion of the disciform stromal lesion became relatively clear, and a ring-shaped opacity resulted. On Aug. 31, 1978, the patient's right eye had been quiet without corticosteroid for six months; visual acuity improved to 6/6 (20/20).

Case 2—A 3-year-old girl suffered from varicella at the beginning of January 1978. Eruptions were distributed on the face, trunk, and extremities. On March 27, 1978, she was febrile and complained of pain around the left ear. The diagnosis of left otitis media was made by her family physician. A regimen of antibiotics was begun, and the patient became asymptomatic in three days. Four days later, the patient's mother noticed hyperemia and corneal haze in the left eye. Herpes simplex keratitis was presumed by an ophthalmologist, who prescribed idoxuridine and gentamicin drops. As the stromal edema increased, topical dexamethasone was added to the regimen on April 5, 1978.

On April 13, 1978, the patient was referred to our clinic. On examination, no scars after eruptions were observed on her face. A mild pericorneal hyperemia in the left eye was noted. The corneal epithelium was edematous, and a disciform stromal opacity, 5 mm in diameter, was seen in the center. Keratic precipitates and folds in Descemet's membrane were present. A tentative diagnosis of herpes simplex disciform keratitis was made. Treatment consisted of 0.5% atropine once a day, idoxuridine drops five times a day, and 0.1% dexamethasone three times a day. Inflammation subsided gradually until April 27, 1978, when a dendritic lesion appeared in the corneal epithelium. It was gray, slightly raised, and stained moderately with fluorescein (Fig. 2). The lesion was similar to that described in Case 1, but much larger in size. The diagnosis was changed to varicella keratitis. The debrided epithelium from the corneal lesion was used for viral examinations. Immunofluorescence was positive for varicella-zoster virus (Fig. 3), and negative for herpes simplex virus. Viral cultures were performed, but no cytopathic effect was observed after three weeks' incubation. The culture of the second passage was also negative for virus. The serum complement-fixing antibody titer was 1:16 for varicella-zoster virus, and less than 1:4 for herpes simplex virus. Dexamethasone drops were discontinued. The debrided epithelial lesions healed on

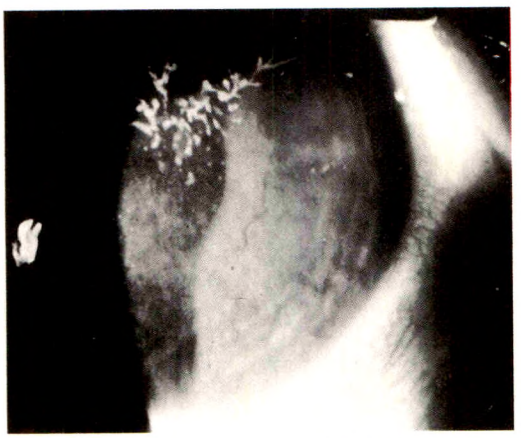

Fig. 2 (Uchida, Kaneko, and Hayashi). Case 2. Varicella epithelial dendritic lesion and stromal nebulae of left cornea.

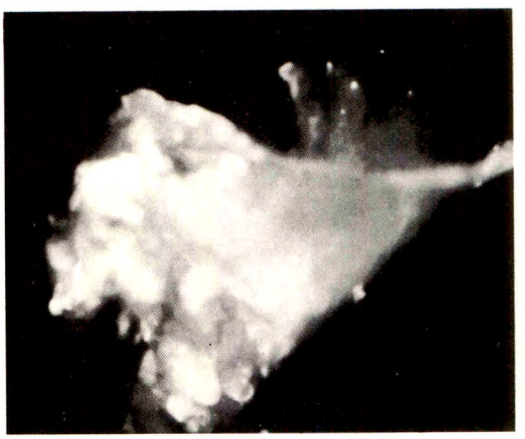

Fig. 3 (Uchida, Kaneko, and Hayashi). Epithelial cells from dendritic lesion of Case 2 stained by direct immunofluorescent method. Note positive fluorescence for varicella-zoster virus (fluorescence microscopy, ×145).

May 4, 1978. One week later, because the stromal haze increased, dexamethasone was reinstituted.

On May 25, 1978, several fragmented dendritic lesions appeared near the temporal corneoscleral limbus. At that time, viral isolation was attempted again, but no virus was grown. The debrided areas healed in four days. The medications were tapered slowly over the next six months. On Nov. 20, 1978, the patient was taking 0.02% dexamethasone, once a day, to suppress smoldering of the stromal edema and iritis. Visual acuity was R. E.: 6/6 (20/20) and L. E.: 6/15 (20/50).

Discussion

Our two patients developed dendritic keratitis approximately four months after the appearance of varicella cutaneous lesions, while their disciform keratitis and iritis were treated with topical corticosteroid, idoxuridine, and atropine drops. The clinical course was almost the same as that described by Nesburn and associates,[4] who showed typical virus-like particles in the corneal epithelium. Of nine patients described by Piebenga and Laibson,[2] eight developed dendritic lesions from one to 20 months after the onset of herpes zoster keratouveitis. We described such a case previously.[6] Most of those patients had been given topical corticosteroids to control keratouveitis. Therefore, corticosteroids apparently had some effect in inducing dendritic keratitis upon the stromal lesion in varicella as well as in herpes zoster.

In contrast, three patients of Pavan-Langston and McCulley[1] developed dendrites during the stage of acute zoster skin lesions. Marsh, Fraunfelder, and McGill[3] divided zoster epithelial keratitis into two groups: acute epithelial dendritic keratitis locates generally in the peripheral part of the cornea; whereas corneal mucous plaque keratitis appears anywhere on the cornea several months after the onset of skin lesions. Occurrence of dendritic lesions during the acute stage of varicella has not been documented, though many ocular manifestations are known.[7,8] If more cases of varicella were seen by ophthalmologists during the acute stage, such dendritic lesions would be encountered.

Zoster dendrites differ from herpes simplex dendrites in the clinical morphology; they are characterized by (1) gray-white plaque-like lesions raised on the surface, (2) coarse, sometimes fragmented configuration without terminal bulbs, and (3) poor or moderate staining with fluorescein. From our experience,

varicella dendrites have essentially the same figure as zoster dendrites. Therefore, the occurrence of dendritic lesions with the above-mentioned appearance in disciform keratitis in children, may indicate the varicella origin of the condition, even when other clinical signs are missing.

Varicella-zoster virus is difficult to isolate from the cornea.[2-4] We failed to recover the virus. Immunofluorescence is another useful method for the etiologic diagnosis of viral diseases. Previously, we reported the direct method to show the viral antigen from the epithelial lesions of herpes zister keratitis.[6] In our two patients presented here, scrapings from the dendritic lesion showed epithelial cells with positive fluorescence for varicella-zoster virus. Therefore, varicella-zoster virus invades the corneal epithelium and causes the dendritic lesion. A positive serum antibody activity for varicella-zoster virus in Case 2 is compatible with varicella infection. A low antibody titer in Case 1 is difficult to explain, but we think virus activity might have decreased during a four-month period after the onset of varicella.

Summary

A 7-year-old boy and a 3-year-old girl suffered from unilateral disciform keratitis and iritis associated with varicella. While they were treated with topical corticosteroid, idoxuridine, and atropine drops, dendritic lesions typical of herpes zoster appeared four months after the onset of eruptive skin lesions. Using the direct immunofluorescent method, we showed varicella-zoster virus antigen in the epithelial cells scraped from the dendritic lesion.

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PUPIL CYCLE TIME IN OPTIC NERVE COMPRESSION

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A small beam or slit of light focused at the pupillary margin will induce regular persistent oscillations of the pupil. The average period of these cycles (the pupil cycle time) may be easily measured and expressed in milliseconds. The pupil cycle time is characteristic for any given individual, and shows little difference between a pair of normal eyes. The theoretical and practical considerations involved in this test, as well as normative data, are presented elsewhere.[1] Prolongation of the pupil cycle time may occur when either the afferent or the efferent limb of the pupillary light reflex is impaired. In a previous report, prolongation of pupil cycle time in patients with optic neuritis was documented.[2] We describe herein changes in pupil cycle time with optic nerve compression and subsequent improvement of the pupil cycle time with decompression. These changes in pupil cycle time are correlated with changes before and after treatment in visual acuity and visual fields.

SUBJECTS AND METHODS

Eleven patients were studied (Figs. 1 and 2). Patients 1 through 9 had chiasmal tumors and were treated with surgery and in some cases with radiation, as noted. Patients 10 and 11 had severe Graves' ophthalmopathy with optic neuropathy and were treated initially with corticosteroids and subsequently underwent orbital decompression. Before and after treatment, measurements were made of the best corrected visual acuity, color vision, and relative afferent pupillary defects. Goldmann perimetry was performed on all patients by perimetrists. In most cases, visual fields before and after treatment were done by the same perimetrist.

Pupil cycle time was measured with the patient seated at a slit lamp in a dimly lit room. A horizontal slit of moderate intensity, 0.5 mm thick, was projected onto the iris just below the pupillary margin. The focused beam was then elevated until it just overlapped the pupillary margin and persistent regular pupillary oscillations were produced. In each eye, at least six runs of ten cycles each were timed with an electronic hand-held stopwatch to the nearest 1 msec. The total elapsed time was divided by the total number of cycles to obtain the pupil cycle time in milliseconds.

It was possible to obtain a pupil cycle time in 15 out of 22 eyes. In this series, eyes that did not cycle always had poor pupillary light reaction, poor visual acuity, and extensive visual field loss.

RESULTS

Nine of 11 patients (1-3, 5, and 7-11) had improved visual acuity or visual fields, or both, after treatment (Figs. 1 and 2). In all of these cases the pupil cycle time improved as well. In most instances the improvement in pupil cycle time was commensurate with the visual improvement. Thus, patients who experienced dramatic improvement in vision

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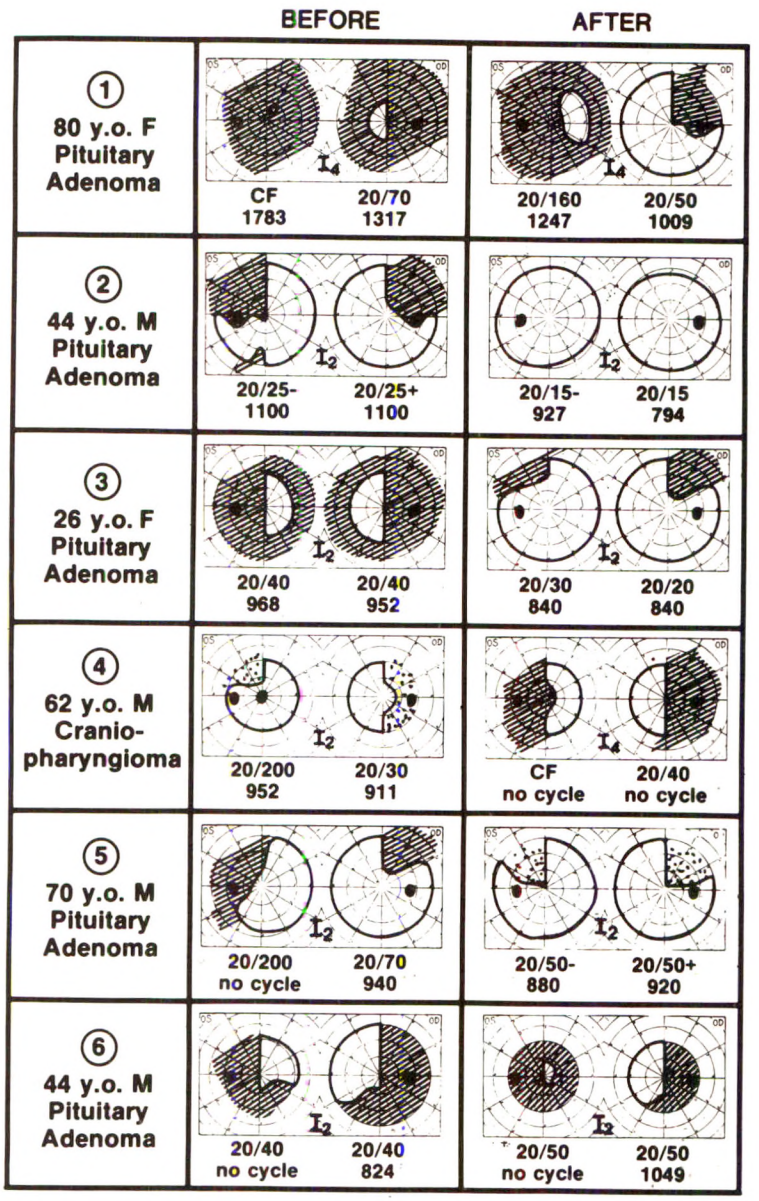

Fig. 1 (Weinstein, Van Gilder, and Thompson). Visual acuity, visual fields, and pupil cycle time before and after treatment in six patients with optic nerve compression. Patients 1 to 6 had chiasmal compression.

also generally had marked improvement in their pupil cycle time (Figs. 1 and 2). In Patients 4 and 6, visual acuity and visual fields worsened after surgery, with a concurrent prolongation of pupil cycle time. Patient 10, with optic neuropathy of Graves' disease, improved at first with corticosteroid treatment but later deteriorated, necessitating orbital decompression. After decompression her visual acuity and visual field again improved and have remained at this level. The fluctuations in her visual acuity and visual fields are paralleled by similar changes in her pupil cycle time (Fig. 3).

Discussion

All of our 11 patients had pupil cycle times that were abnormal in at least one eye; that is, either longer than 954 msec or

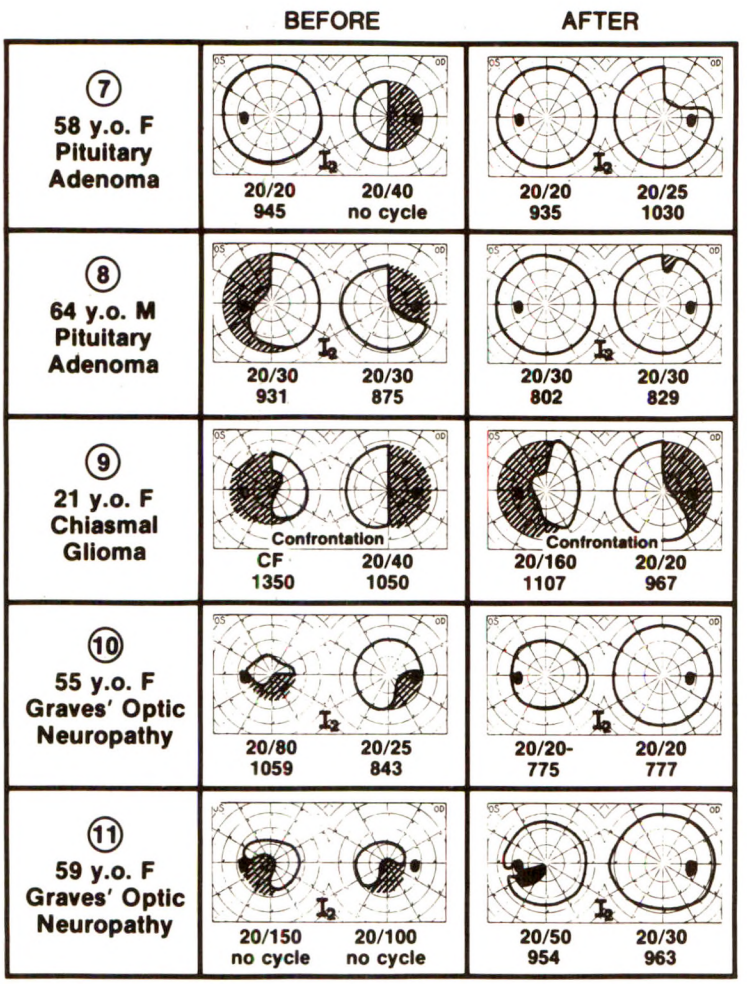

Fig. 2 (Weinstein, Van Gilder, and Thompson). Visual acuity, visual fields, and pupil cycle time before and after treatment in five patients with optic nerve compression. Patients 7 to 9 had chiasmal compression. Patients 10 and 11 had optic neuropathy associated with Graves' disease.

more than 70 msec difference between the two eyes (95% confidence limits).[1] In all cases the change in pupil cycle time before treatment was in the same direction as the change in visual fields and visual acuity, and was generally comparable in magnitude.

When the iris muscles are normally innervated and responsive, the pupil cycle time is apparently dependent on the speed of conduction along the optic nerves and the number and strength of optic nerve impulses. The latency of the visual-evoked response is likewise dependent on the speed of conduction along the optic nerve, and its amplitude is dependent on the number and strength of impulses arriving synchronously at the occipital cortex. Because the pupil cycle time seems to vary with delays in the pupil reflex arc and the visual-evoked response measures the delay in the appearance time of the impulse at the occipital cortex, they both can be used as indicators of conduction delay in optic nerve disease.[2,3–6] Feinsod and associates[7,8] and Halliday and associates[9] have shown that visual-evoked responses are abnormal in compressive optic nerve disease and improve with decompression.

The pupil cycle time, like the visual-evoked response, provides an objective

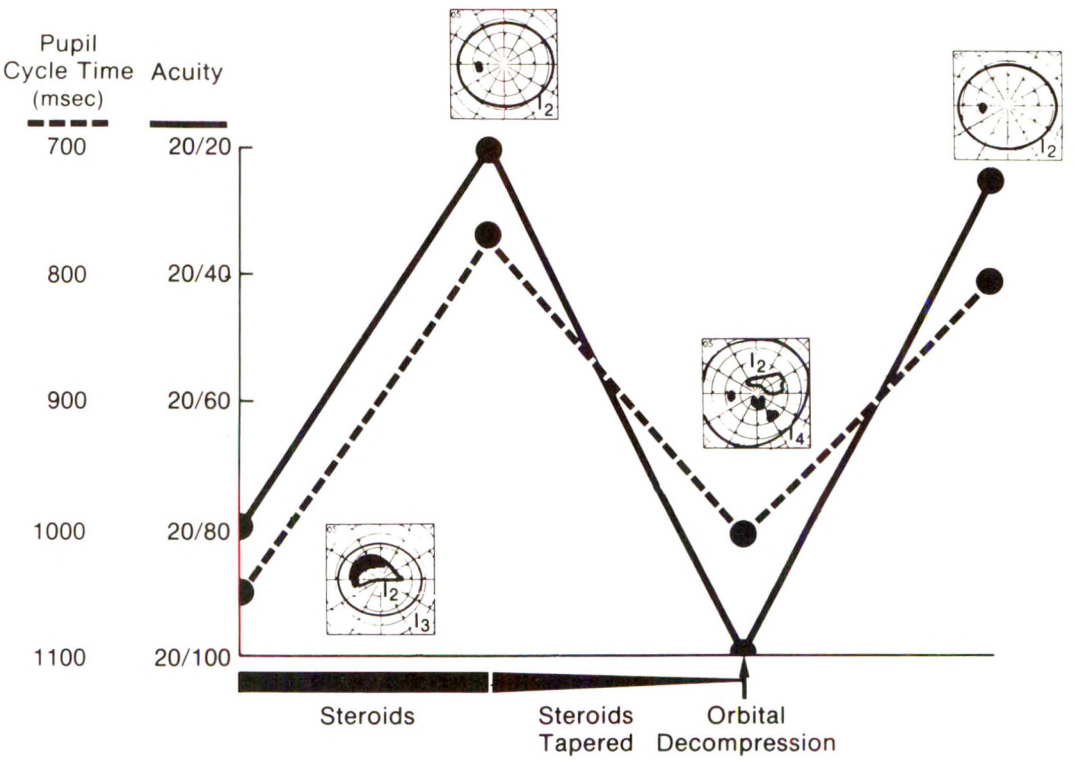

Fig. 3 (Weinstein, Van Gilder, and Thompson). Changes in visual acuity and pupil cycle time in a patient with optic neuropathy associated with Graves' disease. Note improvement of both factors during treatment with systemic corticosteroids, and worsening while corticosteroids were tapered. Both visual acuity and pupil cycle time subsequently improved after orbital decompression.

indication of optic nerve conduction. Although perhaps somewhat less sensitive than the visual-evoked response, the pupil cycle time is much easier to measure and requires less time and equipment. Like the visual-evoked response, the pupil cycle time provides an objective, quantitative index for each eye individually. In this respect, it is superior to the afferent pupillary test, which is perhaps the most frequently used objective clinical test of optic nerve function. The afferent pupil defect is a comparative sign and may not be present when there is matched optic nerve dysfunction in the other eye. Pupil cycle time is measured first in one eye and then the other and may even be used in monocular patients.

Summary

We measured pupil cycle time before and after treatment in 11 patients with compressive optic nerve disease. Nine patients had chiasmal tumors and two had optic neuropathy of Grave's disease. Pupil cycle time before treatment was abnormal in at least one eye of all patients and in each case, pupil cycle time improved or worsened in accordance with the response to treatment of the patient's visual acuity and visual fields. This suggests that the pupil cycle time may be used as a simple objective office test for following up patients with impaired optic nerve conduction as the result of optic nerve compression. This information is similar to that gained from visual evoked response and may be used together with

other objective clinical data such as disk pallor, nerve fiber loss, and relative afferent pupillary defect.

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Ophthalmic miniature

I suddenly heard her utter a sharp yowl and saw that she was rubbing her eye. It was plain to the meanest intelligence that she had gone and got a cinder into it, of which there were several floating about.

It solved the whole difficult problem of how I was ever going to break down the barriers, if you know what I mean, and get acquainted. It so happens that if there is one thing I am good at, it is taking things out of eyes—cinders, flies, gnats on picnics, or whatever it may be. To whip out my handkerchief was with me the work of a moment, and I don't suppose it was more than a couple of ticks later before she was thanking me brokenly and I was not-at-all-ing and shoving the handkerchief up my sleeve again. Yes, less than a minute after I had been practically despairing of ever starting anything in the nature of a beautiful friendship, there I was, fixed up solid.

The odd thing was, I couldn't see any cinder, but it must have been there, because she said she was all right now and, as I say, started to thank me brokenly.

P. G. Wodehouse
Laughing Gas, 1936

HEPATOMA METASTATIC TO THE ORBIT

JANE R. LUBIN, M.D., ARTHUR S. GROVE, JR., M.D., Z. NICHOLAS ZAKOV, M.D., AND DANIEL M. ALBERT, M.D.

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Cases of hepatoma metastatic to the eye are rare. Bock[1] published the first case report of a hepatocellular carcinoma metastatic to the choroid in 1885. A clinically deep green lesion of the fundus, which looked like hepatoma histologically, was proven chemically to secrete biliverdin. No description of the primary tumor was included. In a second reported case,[2] pathologic examination was not performed. Oatman[3] described a case of a 56-year-old man with a primary liver adenocarcinoma metastatic to the choroid, optic nerve, and sclera. Orbital involvement in this case was presumably by direct extension from the choroidal mass. The involved eye showed a detached retina and secondary glaucoma. Metastases from the liver tumor were also found in the lungs, spleen, kidney, and lymph nodes. The diagnosis was made at autopsy. Taake, Allen, and Straatsma[4] described a hepatoma metastatic to the choroid with extensive pathologic documentation.

Several clinically diagnosed cases of hepatoma metastatic to the orbit have been described. In Mortada's[5] series of eight cases of orbital metastasis, a 40-year-old woman had right proptosis, with a superior rectus metastasis from a bile duct type carcinoma of the liver, with no evidence of tumor by skull x-ray and orbital films; therefore, this was probably not an extension from a cerebral metastasis. He gave no histologic confirmation of the diagnosis. Jensen,[6] in his Danish study, also stated that he had seen such a case. To date, there have been no published reports of a histologically proven hepatocellular carcinoma metastatic to the orbit.

Hepatomas do not occur often in the United States population. Becker[7] reported the incidence by autopsy studies to be 0.1 to 0.7% of all tumors. High-risk areas of the world include Southeast Asia and the sub-Sahara area. This high incidence is thought to be related to such factors as malnutrition, parasitic infestation, excess iron intake, amebiasis, and most recently, aflatoxin, a fungal product of *Aspergillus flavus*. However, in the United States, the incidence of hepatoma is clearly related to the intake of alcohol and the presence of cirrhosis, particularly the macronodular variety. Of patients with cirrhosis, 4 to 6% eventually develop hepatoma,[8] and conversely, 85.4% of patients with hepatoma also have cirrhosis. In patients with hemochromatosis (in which cirrhosis eventually develops), the incidence of hepatoma is twice that in patients with cirrhosis only. It was recently noted[9] that 31.7% of patients with hepatoma also have hepatitis B-associated antigen. Patients with alpha-1 antitrypsin deficiency also seem more likely to develop hepatoma than the general population.

Only 15 to 25% of liver tumors are of bile duct origin. The rest are of liver parenchymal origin, with variable degrees of anaplastic appearing cells. Hepatoma most commonly metastasizes to the lung (34 of 41), brain (four of 41), and bone (14

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Fig. 1 (Lubin and associates). Left, Initial presentation of the patient, showing right proptosis. Right, View of right proptosis from above.

of 41).[10] Recently, a case of hepatocellular carcinoma with metastasis to the jaw was reported, which manifested as a draining sinus.[11]

We describe herein the case of a man with a history of cirrhosis of the liver and unilateral progressive right proptosis. A diagnosis of hepatocellular carcinoma was made. To the best of our knowledge, this is the first histologically proven case of hepatoma metastatic to the orbit.

Case report

A 69-year-old man, born in Georgia, with a history of excessive alcohol intake, tuberculosis treated with isoniazid and ethambutol, and a history of latent syphilis, came here with slowly progressive right proptosis of three to four months' duration (Fig. 1). The patient had no other complaints.

Physical examination revealed an alert man with proptosis of the right eye. The best corrected visual acuity was counting fingers at three feet in both eyes, and no cranial nerve palsies were noted. His neck was supple; no lymphadenopathy was evident. Lungs were clear. Auscultation of the heart revealed a grade 2/6 systolic murmur. His abdomen was soft, with some tenderness in the right upper quadrant, without rebound. The liver edge was palpable 3 cm below the right costal margin, and was firm and nodular. This finding had been unchanged since 1971. His extremities showed minimal clubbing of the fingers. Results of laboratory studies included the following: hemoglobin, 10.8 g/100 ml; white blood cell count, 19.6 cells/mm^3, 85% polymorphonuclear leukocytes, one band, five lymphocytes, one monocyte; blood urea nitrogen, 8 mg/100 ml; creatinine, 0.7 mg/100 ml; blood glucose, 100 mg/100 ml; total bilirubin, 0.7 mg/100 ml; direct bilirubin, 0.3 mg/100 ml; serum glutamic-oxaloacetic transaminase, 24 IU/l; alkaline phosphatase, 30 IU/l; lactic dehydrogenase, 100 IU/l; 5′ nucleotidase, 1.7 IU/100 ml (all within normal limits); total protein, 8.3 g/100 ml; albumin 3.3 g/100 ml; globulin slightly high at 5.0 g/100 ml; calcium and phosphorus, normal. No alpha-fetoprotein was detected in the patient's serum.

Orbital ultrasonography (Fig. 2) revealed a superior posterior mass with good sound transmission, suggesting a cystic orbital tumor or necrotic mass. Best corrected visual acuity was recorded in the chart 25 years ago as 6/60 (20/200) in both eyes (diagnosed as primary optic atrophy), and on recent examination, visual acuity was counting fingers at three feet bilaterally.

Fluorescein angiography (Fig. 3) disclosed an area of alternating hyperfluorescence and hypofluorescence, typical of choroidal folds, superotemporal to the disk, without leakage or staining of fluorescein. Computed axial tomography (Fig. 4) revealed a right intraorbital mass, extraconal in location, displacing the globe laterally and inferiorly, without evidence to suggest bone erosion either adjacent to, or distant from, the orbital mass. Supra- and infratentorial regions were normal. Sinus and skull films gave the impression of a soft tissue swelling over the right orbit, with destruction of the medial portion of the orbital rim and increased density in the right frontal sinus. Biopsy of the orbital mass revealed a solid tumor, diagnosed histologically as hepatoma based on the following: the cord-like arrangement of the cells, the basement membrane lining these cords in some areas with poorly defined endothelial cell lining, the abundant granular eosinophilic cytoplasm, and the presence of glycogen granules on PAS stain.

Seven years before admission, the patient had had a barium enema that revealed only colonic polyps.

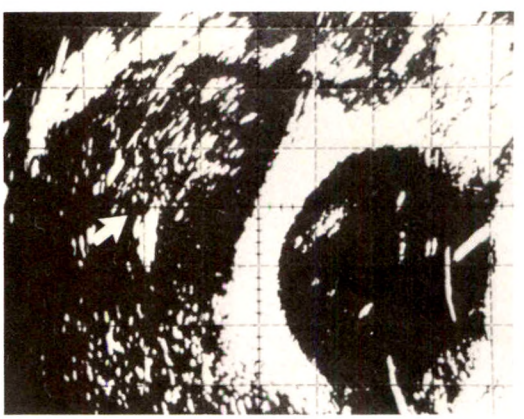

Fig. 2 (Lubin and associates). Orbital ultrasonography reveals superior posterior mass (arrow) having an intraconal location, with good sound transmission.

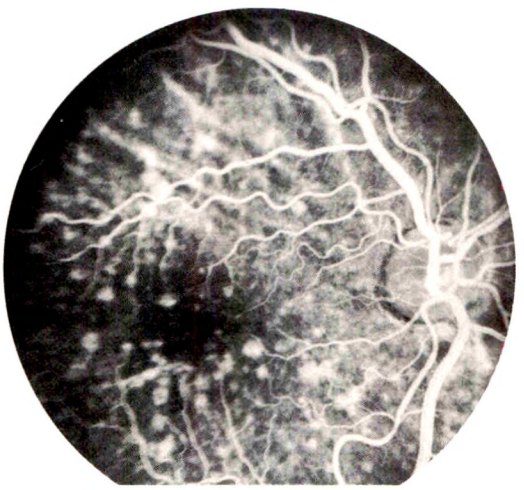

Fig. 3 (Lubin and associates). Fluorescein angiogram showing choroidal folds superotemporally without leakage or staining of the dye.

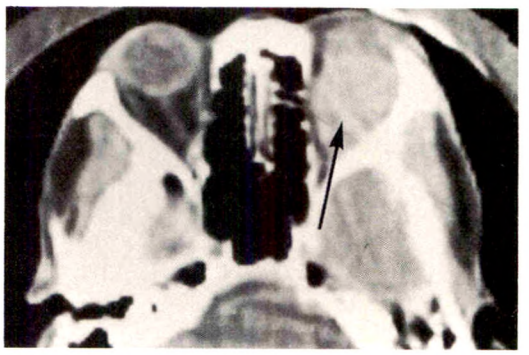

Fig. 4 (Lubin and associates). Computed tomography scan showing extraconal mass (arrow) displacing the globe laterally and inferiorly, with no evidence of bone destruction.

Results of an upper gastrointestinal series were negative. Intravenous pyelogram was read as compatible with medullary sponge kidney or papillary necrosis. Also noted was a calyceal diverticulum in the right upper pole. Because of long-standing hepatomegaly and anemia, the patient at that time also had a liver biopsy, which showed portal infiltrates of lymphocytes, occasional plasma cells and macrophages, and a parenchyma with focal hepatic cell necrosis with inflammatory cell infiltrates. In focal areas, the portal zones suggested early fibrosis. These findings are consistent with early Laennec's cirrhosis. No evidence of tumor was found.

The patient underwent tests to locate primary tumor. Results of a barium enema and upper gastrointestinal study were negative. Intravenous pyelogram revealed a calcified right upper lobe abnormality, a cold abscess with central calcifications, strongly suggestive of renal tuberculosis, but malignancy could not be eliminated. Liver-spleen scan was consistent with hepatocellular disease, although a few ill-defined filling defects were noted in the right lobe. The spleen was slightly enlarged. Bone scan showed focal areas of increased activity in the femurs (matching areas of destructive lesions on x-ray). No abnormal activity was noted in the skull. Chest x-ray showed fractures of the sixth and eighth ribs, without a history of trauma.

The patient developed fever, abdominal pain, nausea, and vomiting. Plain films of the abdomen revealed calcified right upper quadrant stones, and a diagnosis of acute cholecystitis was made. The patient was taken to the operating room for cholecystectomy. Exploratory laparotomy revealed a normal stomach, small bowel and colon, and an enlarged but otherwise normal spleen. The liver was small and contained nodules of hepatic tissue. A 2.5 × 3-cm white nodule was discovered on the underside of the caudate lobe of the liver. A biopsy specimen was taken of the nodule. A urologic surgeon examined the right upper lobe of the kidney for the possibility of extension of tumor into the liver from this source. The kidney was normal. No biopsy specimen was taken.

Histologic sections of the liver biopsy specimen and orbital mass (Figs. 5 and 6) showed similar findings. The wedge of liver tumor showed cells arranged in cords, two to three cells wide. These trabeculae were ill-defined, but in places, a thin basement membrane could be discerned covering the bands of cells. Endothelial cells lined the sinuses. The cells were variable in size, with large, hyperchromatic nuclei, prominent nucleoli, and abundant granular eosinophilic cytoplasm with areas of hyaline material, probably representing Mallory's hyaline.[12] No area of normal hepatic parenchyma accompanied the specimen. The orbital

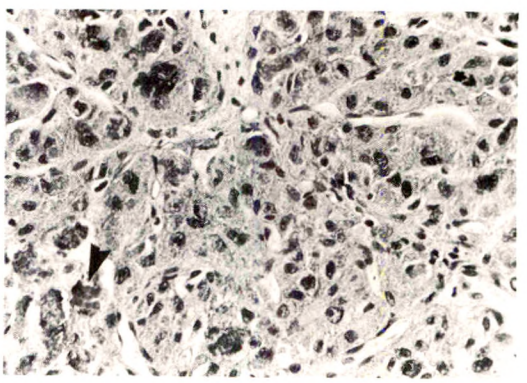

Fig. 5 (Lubin and associates). Liver biopsy showing the characteristic features of hepatoma; cords of atypical parenchymal cells with hyperchromatic nuclei, and abundant granular eosinophilic cytoplasm. Mallory bodies are seen (arrowhead) (hematoxylin and eosin, ×470).

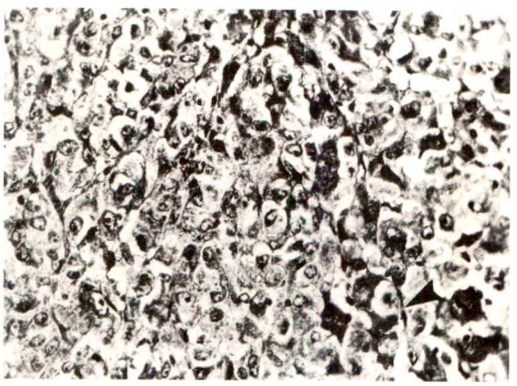

Fig. 6 (Lubin and associates). Orbital biopsy showing the same features seen in Figure 5, but with somewhat more anaplastic appearing cells, more marked and atypical. Areas of basement membrane with endothelial cell lining can be seen (arrowhead) (Masson trichrome, ×470).

specimen showed more bizarre, variably sized cells than the liver nodule. More atypical mitoses were noted. Trabeculae were even less well defined, and there were only traces of basement membrane, with little evidence of an endothelial lining. Periodic acid-Schiff staining revealed the presence of glycogen granules. No bile staining was seen on either specimen, and there was no calcification of stroma. Electron microscopy was done on the orbital tumor, which showed abundant glycogen, mitochondria, and endoplasmic reticulum in the cytoplasm, and the presence of poorly defined basement membrane-lined sinuses with endothelial cells, confirming the diagnosis of hepatoma.

Palliative radiotherapy only was given. The patient received 3,000 rads in two weeks to the right orbit. No chemotherapy was given at the patient's request. The orbital mass regressed significantly after completion of the course of radiotherapy.

Discussion

Although brain metastases from hepatocellular carcinoma are relatively common and this tumor tends to metastasize to the flat bones of the jaw and skull, this case is unusual because it metastasized to the orbit. No evidence could be found by computed axial tomography scan, bone scan, or orbital roentgenography that this orbital mass originated from a bone metastasis. Erosion around the orbital rim was thought to be secondary to the expanding nature of the lesion. Although no histologically proven cases of this nature appear in published reports, we have recently heard of a similar case from Houston, Texas, with exophthalmos as the initial symptom of a hepatoma (Richard T. May, M.D., personal communication, May 1978).

Metastasis of tumors to the orbit occurs much less frequently than metastasis to the globe. Pathologic series by Hart,[13] Jensen,[6] and Bloch and Gartner[14] have confirmed the clinical observation that the incidence of involvement of metastatic carcinoma to the orbit is one-fifth that of metastatic carcinoma to the eye. In his survey of published reports, Rose[15] found only 51 reports of metastatic carcinoma to the orbit before 1965. Since 1950, 61 patients with metastases to the orbit and eyelid have been described.[16] In contrast, by 1936, Lemoine and McLeod[17] had already found 230 reports of patients with carcinoma metastatic to the eye.

From another point of view, metastatic carcinoma rarely appears as an expanding lesion of the orbit producing exophthalmos. In his series of 230 consecutive patients with exophthalmos, Moss[18] found only one patient who had a metastatic carcinoma to the orbit. Silva[19] reported a similar series of 300 consecutive patients with clinical exophthalmos. When surgical biopsy specimens were taken only seven of them had metastatic carcinoma (incidence = 2.3%). Reese,[20] in a series of 877 consecutive cases of orbital neoplasms, found 29 to be metastatic in nature (incidence = 3%). Henderson[21] reported from the Mayo Clinic series (1948 to 1966) a total of 32 metastatic carcinomas among 465 orbital tumors (incidence = 7%).

In 1953, Ingalls[22] had 216 patients with tumors (and pseudotumors) of the orbit, and found three to be of metastatic origin. Spaeth,[23] in a statistical analysis of 170 cases of ocular malignancy, included four patients with ocular metastasis from distant primaries. Recently, Font and Ferry[24] studied 227 cases of carcinoma

metastatic to the eye and adnexae from the Armed Forces Institute of Pathology files, and among these cases, found 28 that were metastatic to the orbit. The ratio of ocular to orbital involvement was 7:1 (or an incidence of 12%).

Most authors agree[6,16,24] that the most frequent sites of origin for metastatic carcinoma to the eye and ocular adnexae include the following: (1) breast, and (2) lung, with genitourinary tract and gastrointestinal tract also common primary sites. However, a wide range of primary tumors may metastasize to the eye. The eye or orbit may not infrequently be the first site of malignant spread, and ocular symptoms occasionally precede the diagnosis of primary tumor. In 60% (17 of 28) of cases in Font and Ferry's series,[24] orbital symptoms preceded the symptoms of the primary lesion. This was also true in our case.

Font and Ferry[24] found immediate symptoms of orbital metastasis of carcinoma, in order of frequency, to include the following: exophthalmos, 75%; pain, 29%; decreased vision, 29%; periorbital swelling, 25%; a visible mass, 21%; and ophthalmoplegia and diplopia, 18%. They found no preponderance of either left- or right-sided orbital metastases.

Of the eye and adnexae, the orbit is the second most frequent site of involvement by metastatic carcinoma (after the posterior segment of the eye).[24] The orbital muscles are the usual site,[25] and less commonly, the orbital bones.

Summary

A 69-year-old man with a history of cirrhosis of the liver had unilateral progressive proptosis without jaundice, abdominal pain, or gastrointestinal symptoms. Results of laboratory and radiographic studies were also normal. Orbital biopsy revealed hepatocellular carcinoma. Although hepatocellular carcinoma has often been shown to metastasize to the brain and often to the flat bones of the skull, to the best of our knowledge, this is the first histologically proven case of hepatoma metastatic to the orbit.

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OPHTHALMIC MINIATURE

The enemy were so frightened when they saw me, that they leaped out of their ships and swam to shore; I then took my tackling, and fastening a hook to the hole at the prow of each, I tied all the cords together at the end. While I was thus employed, the enemy discharged several thousand arrows, many of which stuck in my hands and face; and, besides the excessive smart, gave much disturbance in my work. My greatest apprehension was for mine eyes, which I should have infallibly lost, if I had not suddenly thought of an expedient. I kept, among other little necessities, a pair of spectacles, in a private pocket which, as I observed before, had escaped the Emperor's searchers. These I took out, and fastened as strongly as I could upon my nose, and thus armed, went on boldly with my work, in spite of the enemy's arrows, many of which struck against the glasses of my spectacles, but without any effect other than a little to discompose them.

Johnathan Swift, *A Voyage To Lilliput*

ORBITAL FINE NEEDLE ASPIRATION BIOPSY WITH B-SCAN GUIDANCE

THOMAS C. SPOOR, M.D., JOHN S. KENNERDELL, M.D., ANDREW DEKKER, M.D., BRUCE L. JOHNSON, M.D., AND PAUL REHKOPF, C.C.E.

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Fine needle aspiration biopsy has been used for the diagnosis of neoplasm in a variety of organs.[1–6] Recently, Schyberg[7] and Westman-Naeser and Naeser,[8] applied this technique to orbital tumors. We have reported its successful use in patients with a variety of orbital lesions,[9] including the use of computed tomography scanning to accurately localize the aspirating needle tip, which is especially useful in neural tumors.[10] We now report the expansion and simplification of this technique by using B-scan ultrasonography in directing fine needle aspiration biopsy of retrobulbar orbital neoplasms.

METHODS

The technique of fine needle aspiration biopsy using a fine-gauge needle has been described by Einhorn and Franzen,[3] and its modification for orbital biopsy, including using computed axial tomography imaging as a guide, was recently described, as used in our hospital.[10]

Ultrasound imaging is done with the Charles Ultrascan. This instrument displays a real time B-scan ultrasonic image that allows the physician to observe the tip of the aspirating needle as it advances and enters the tumor, at which time the aspiration is performed.[10]

Fine needle aspiration biopsy allows preparation of cytologic smears that are stained with the Papanicolaou technique or hematoxylin and eosin. Also, hematoxylin and eosin stained histologic slides can be prepared from paraffin blocks (cell blocks) derived from wire extraction of the remaining fine needle contents.[9]

To date, 24 fine needle aspiration biopsy specimens have been done from 20 patients; that is, including eight from the optic nerve tumors. Ultrasonic imaging has only been used in recent cases.

CASE REPORTS

Case 1—An 84-year-old woman had a 6-mm left proptosis resulting from a superotemporal retrobulbar orbital mass. She had no visual or oculomotor dysfunction. A computed axial tomography scan showed a large superotemporal orbital tumor extending nearly to the orbital apex (Fig. 1). There were no osseous abnormalities in plain skull x-ray films and tomograms. The irregularly contoured dense mass was clearly visible with B-scan ultrasonography (Fig. 2). Because of the patient's age and reluctance to undergo surgery, we decided to do fine needle aspiration biopsy directed by B-scan sono-

Fig. 1 (Spoor and associates). Case 1. Computed axial tomography scan American Science and Engineering 510 matrix showing a superior mass in the right orbit.

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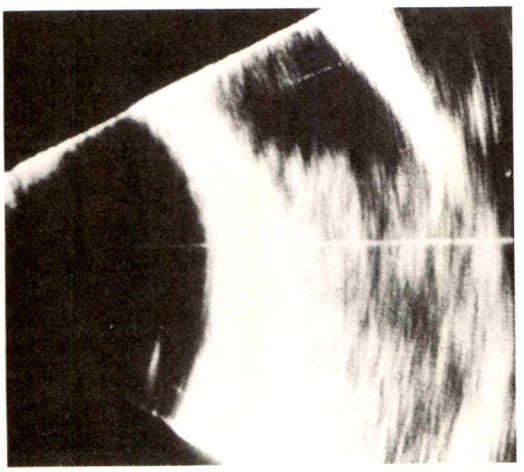

Fig. 2 (Spoor and associates). Case 2. B mode ultrasonogram (ultrascan) showing acoustically homogeneous (sonolucent) mass in supero-orbit.

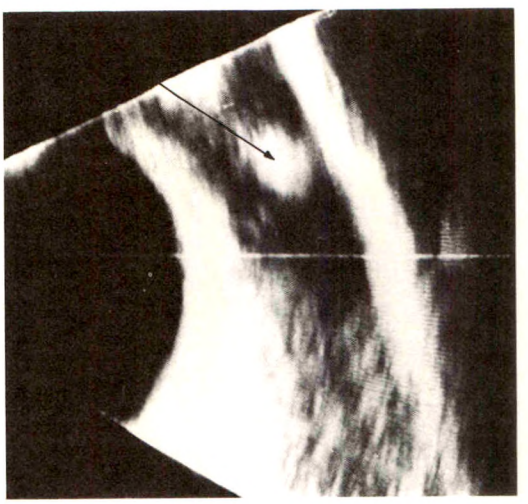

Fig. 3 (Spoor and associates). Case 2. B-scan ultrasonogram showing biopsy needle tip (arrow) in tumor mass.

graphic imaging. After needle localization in the mass (Fig. 3), a specimen was aspirated and examined cytologically. Atypical sheets of well differentiated lymphocytes were seen in the aspirate (Fig. 4) compatible either with lymphoid hyperplasia or well-differentiated malignant lymphoma.

On systemic evaluation, malignant lymphoma, lymphocytic type, was found in the bone marrow biopsy. Treatment consisted of radiation (3,000 rads in ten divided doses) to the orbit combined with chemotherapy.

One month after treatment, the proptosis regressed, and no evidence of orbital lymphoma was apparent, including a normal computed axial tomography scan.

Case 2—A 54-year-old man had a one-week history of slowly decreasing vision in his right eye. He had a 1 1/2-year history of acute myelogenous leukemia presently in remission. He was being treated with a regimen consisting of vincristine, cyclophosphamide (Cytoxan), and daunorubicin (Daunomycin) at bimonthly intervals. Examination disclosed visual acuity of hand motions, an afferrent pupillary defect, absent color vision, a marked visual field loss, and restriction of extraocular motility. The optic disk, posterior pole, and peripheral fundus were normal. Visual acuity rapidly deteriorated to no light perception in the right eye.

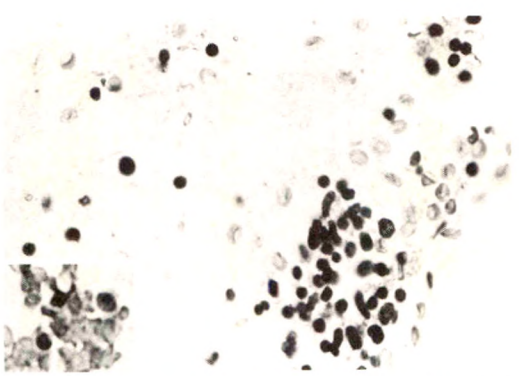

Fig. 4 (Spoor and associates). Case 1. Cell block of fine needle aspiration biopsy with group of well differentiated lymphocytes and a few red blood cells. Inset, Smear with a few well-differentiated lymphocytes (hematoxylin and eosin, ×788; inset, Papanicolaou stain, ×788).

An enlarged optic nerve was detected by B-scan ultrasonography and was confirmed by computed axial tomography scanning. A cytologic specimen of the right optic nerve was obtained by aspiration, under sonographic guidance.

Typical blast cells were seen in the aspirate, compatible with acute myelogenous leukemia (Fig. 5), indicating leukemic invasion of the optic nerve. The patient was treated with local radiation therapy and systemic chemotherapy. There was subsequent improvement in extraocular motility and alleviation of pain, but no improvement in visual acuity.

Case 3—A 57-year-old woman with known carcinoma of the breast was referred for evaluation of decreased visual acuity, diplopia, and proptosis. A computed axial tomography scan showed a posterolateral right orbital mass that was also detected with B-scan ultrasonography. Because of the patient's debilitated state, we attempted to confirm the clinical impression of metastatic disease with fine needle aspiration biopsy directed by using B-scan sonographic imaging, which was done successfully (Fig. 6).

Discussion

These cases show the usefulness of fine needle aspiration biopsy localized with

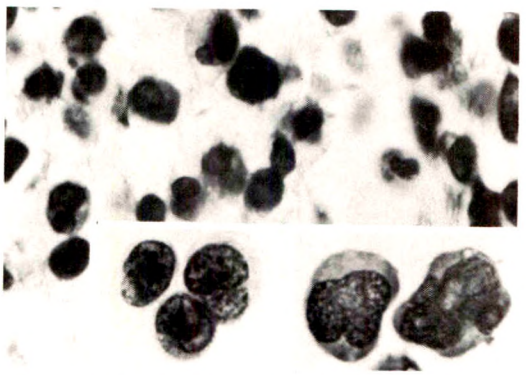

Fig. 5 (Spoor and associates). Case 2. Cell block of fine needle aspiration biopsy with group of blast cells of the myeloid series with high nucleus/cytoplasm ratio and folded nuclei. Left inset, smear stained with Papanicolaou stain. Clumped and irregular chromatin is seen. Right inset, air-dried and Wright-stained smear. Note cells with large folded nuclei with rim of amphophilic cytoplasm (hematoxylin and eosin, ×788; insets, ×1,750).

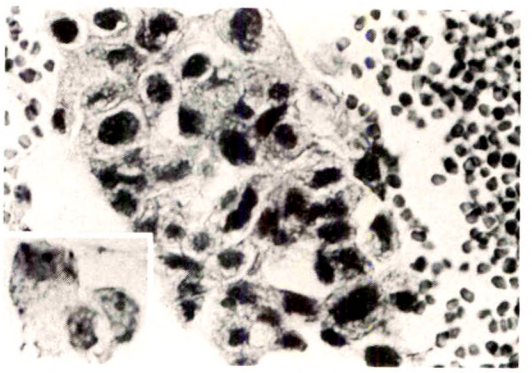

Fig. 6 (Spoor and associates). Case 3. Cell block of fine needle aspiration biopsy with group of neoplastic cells with bubbly cytoplasm and a distinctly glandular pattern consistent with adenocarcinoma. Inset, Neoplastic cells in smear with irregular nuclei and large nucleoli, diagnostic of malignant cells (hematoxylin and eosin, ×788; inset, Papanicolaou, stain, ×788).

B-scan sonographic imaging in obtaining a cytologic diagnosis in distinctly different deep orbital tumors, where proper diagnosis has varied clinical implications.

The fine needle aspiration biopsy diagnosis of possible malignant lymphoma in the orbit that was made in Case 1 prevented the risk of exploratory surgery in an elderly woman. This allowed institution of appropriate clinical evaluation and treatment. The cytopathologist may not be able to distinguish between a well-differentiated malignant lymphoma or benign lymphoid hyperplasia, as in this case; the treatment, however, for the orbital manifestations of either entity in our hands is the same; that is, radiation therapy.

The patient with leukemia (Case 2) was ostensibly in remission and under close medical supervision. Our patient had a clinical appearance of retrobulbar neuritis (presumed ischemic), which rapidly progressed to total visual loss and an immobile globe in the absence of other ocular signs. Such isolated orbital involvement has not been seen in a large series of reported leukemic patients.[11] Ocular and neurologic changes are known to occur during periods of remission after treatment.[12] The occurrence of optic nerve and motility disorders, however, in the absence of choroidal involvement, is rare. Several authors have stressed the importance of rapid diagnosis and prompt radiation therapy in preserving vision in patients with leukemic infiltration of the optic nerve,[11,12] which must be differentiated from visual loss and motility disturbances secondary to chemotherapy.[13] The combination of fine needle aspiration biopsy and B-scan ultrasonography enabled us to obtain a tissue diagnosis, albeit too late to save the patient's vision.

Case 3 represents a debilitated patient with a known primary adenocarcinoma of the breast, with visual loss and an obvious orbital mass lesion. Although breast carcinoma is known to metastasize to the orbit, fine needle aspiration biopsy enabled us to confirm our clinical impression and rule out a more immediately treatable lesion, without exploratory orbital surgery.

We have previously reviewed[9] in detail

the merits and limitations of fine needle aspiration biopsy in orbital disease and the cytologic criteria needed to determine malignancy with this technique. We have also reported the value of fine needle aspiration biopsy guided by computed axial tomography scanning to localize the aspirating needle tip accurately.[10] The use of B-scan ultrasonography simplifies this technique in accessible midorbital retrobulbar lesions to the extent that it can be accomplished as an office procedure. Incisional biopsy is easy to accomplish in eyelid tumors, but more difficult, with increased risk, in deeper orbital tumors.

Fine needle aspiration biopsy of extraconal retrobulbar masses can be done without computed tomography or ultrasonic guidance. In deeper intraconal masses, however, their location must be determined to insure accurate placement of the aspirating needle. Our cases show that such localization and placement can be accurataly done by sonographic imaging. More precise localization is possible with computed axial tomography scanners; but this is time consuming, expensive, and requires more personnel. We still recommend computed axial tomography imaging for biopsy of neural tumors in blind eyes and deeply situated orbital masses because of the limitation of ultrasonic imagery in that area. B-scan imaging enables the physician to rapidly and accurately perform fine needle aspiration biopsy of mid and anterior orbital tumors with close cooperation of a skilled cytopathologist and an ophthalmic pathologist.

None of the three patients described had complications secondary to fine needle aspiration biopsy.

Summary

In three patients we used B-scan ultrasonography to guide the placement of an aspirating needle, which allowed rapid and accurate cytologic diagnosis of retrobulbar orbital neoplasms. This technique spares the patient the greater cost, inconvenience, and morbidity of more invasive procedures.

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COMPUTED TOMOGRAPHY AND ANGIOGRAPHY IN THE DIAGNOSIS OF SUPRASELLAR MASS LESIONS

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We describe herein four cases in which the differentiation between a noncalcified suprasellar aneurysm and tuberculum meningioma, and a calcified suprasellar aneurysm and a craniopharyngioma, could not be determined by computed tomography scan alone. Cerebral angiography clearly showed both aneurysms.

CASE REPORTS

Case 1—A 70-year-old woman had visual impairment in the left eye of two to three months' duration. Examination revealed best corrected visual acuity of R.E.: 6/12 (20/40) and L.E.: 3/60 (8/200). Impairment of color perception in the left eye was evident. Results of visual field examination were normal in the right eye, but revealed a central scotoma and an inferior altitudinal visual field defect in the left eye. Results of ophthalmoscopic examination were normal in the right eye and revealed optic atrophy in the left eye. Plain skull films and optic foramen views were unrevealing. Computed tomography scan revealed a well-circumscribed homogeneously enhancing suprasellar mass arising just medial to the left anterior clinoid (Fig. 1, top). Cerebral angiography showed a large aneurysm (4 × 4 × 4 cm) arising from the left internal carotid artery just distal to the origin of the ophthalmic artery (Fig. 1, bottom). Surgery was not performed.

Case 2—A 67-year-old woman had progressive visual impairment. She reported decreased vision in the left eye since childhood and recent decrease in vision in the right eye for four to five months before examination. Examination revealed best corrected visual acuity of R.E.: 1/60 (3/200) and L.E.: 6/60 (20/200). No impairment of color perception was evident. An afferent pupillary defect in the right eye was noted. Visual field examination revealed an altitudinal depression in the right eye superiorly associated with more significant depression in the superior temporal quadrant. Visual field on the left revealed depression of the superior temporal quadrant, particularly with red targets. On ophthalmoscopic examination there was pallor of the optic disks bilaterally. Plain skull films were unrevealing. Computed tomography scan revealed a round region of increased density in the anterior suprasellar region that enhanced uniformly (Fig. 2). Angiography showed an avascular extra-axial mass located just above the tuberculum sella. At surgery, a large tuberculum and diaphragma sella meningioma was removed. The optic nerves were raised and the optic chiasm was displaced posteriorly by the tumor. Postoperatively both visual acuity and visual field function improved.

Case 3—A 53-year-old-woman had progressive loss of vision bilaterally of several months' duration. Complete blindness in the left eye and a temporal visual field defect in the right eye were noted. Plain skull films showed a curvilinear calcification in the supra- and retrosellar region (Fig. 3). Computed tomography scan revealed a large area of calcification in the posterior suprasellar region (Fig. 4, left). After intravenous contrast injection, enhancement of the anterior part of the lesion with a persistent area of isodensity in the center was noted (Fig. 4, right). Carotid angiography showed a large, partially thrombosed aneurysm of the carotid artery (Fig. 5). The aneurysm was ligated at surgery and the thrombus was evacuated. Postoperatively the patient developed a transient right hemiparesis and mild aphasia from which she partially recovered. No change in visual fields or visual acuity was noted.

Case 4—A 47-year-old woman had a one-year history of frontal headaches and blurred vision. Examination revealed a bitemporal visual field defect and papilledema. Visual acuity was R.E.: 6/15 (20/50) and L.E.: 6/60 (20/200). Results of plain film examination of the skull were normal. Linear tomography showed faint stippled suprasellar calcification. Computed tomography scan showed a round nonhomogeneously enhancing suprasellar mass with areas of calcification noted on the precontrast scan (Fig. 6). Cerebral angiography revealed an avascular suprasellar mass. At surgery, a craniopharyngioma was removed. No significant clinical change was noted postoperatively.

DISCUSSION

Numerous reports concerning the usefulness and sensitivity of computed scan-

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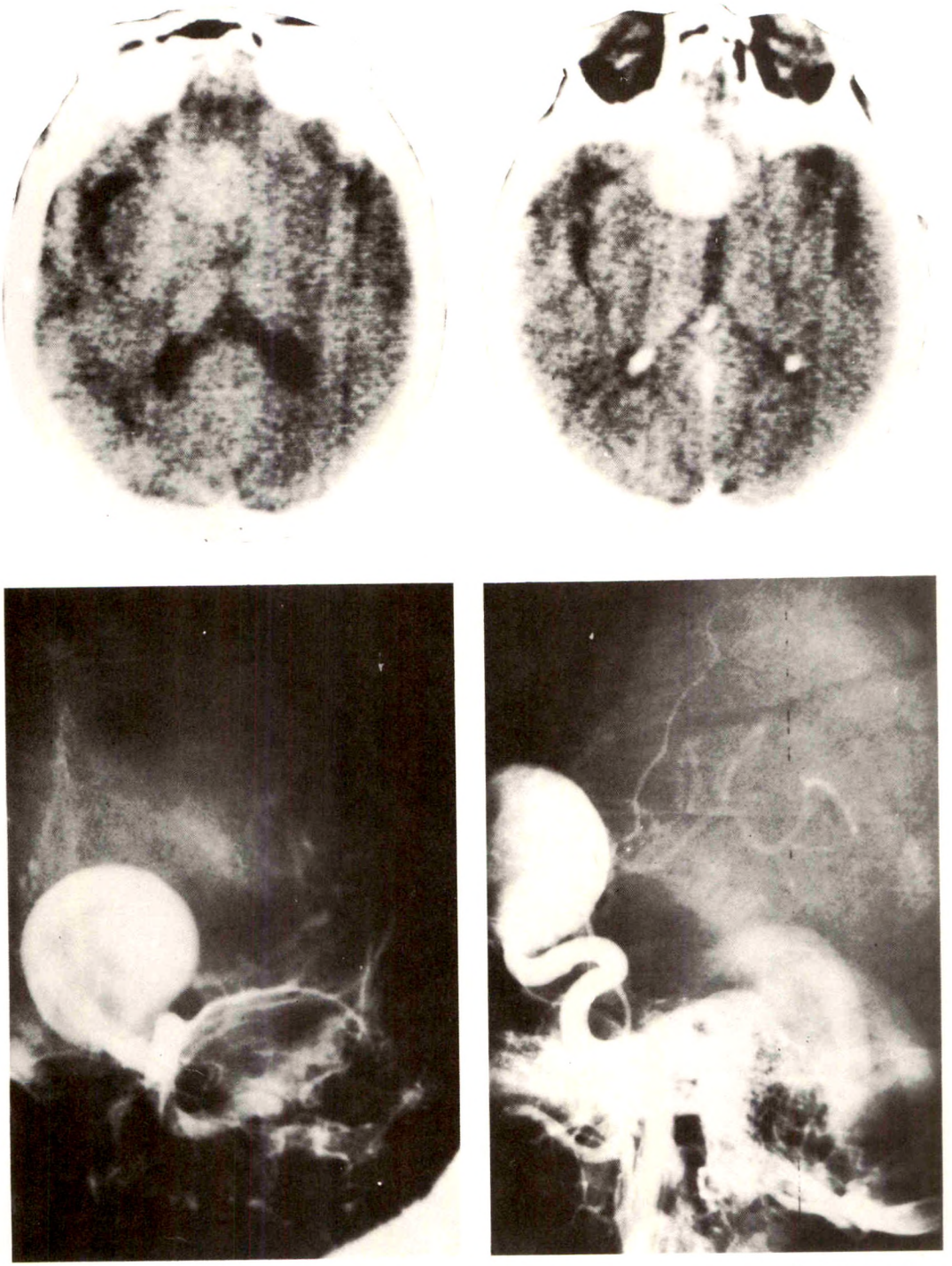

Fig. 1 (Kokoris, Rothman, and Wolintz). Case 1. Giant intracranial aneurysm (noncalcified). Precontrast (top left) and postcontrast (top right) enhanced scans show a large homogeneously enhancing suprasellar mass adjacent to the left anterior clinoid. Anteroposterior (bottom left) and lateral (bottom right) left carotid angiogram reveal the aneurysm arising from the internal carotid artery just distal to the origin of the ophthalmic artery.

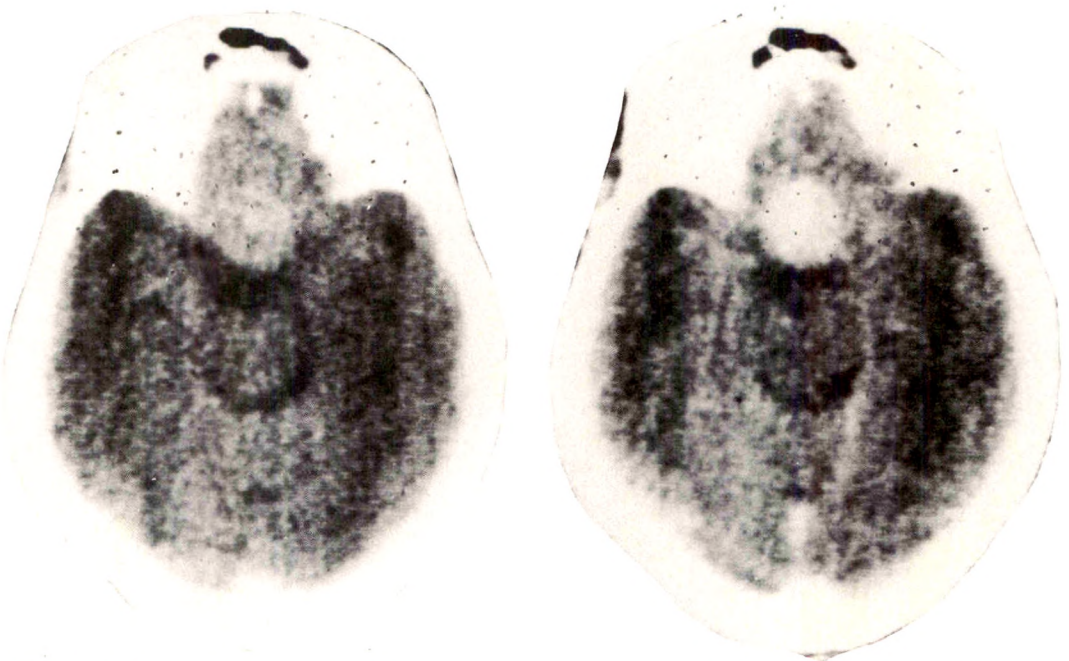

Fig. 2 (Kokoris, Rothman, and Wolintz). Case 2. Tuberculum and diaphragma sella meningioma. Precontrast (left) and postcontrast (right) enhanced scans again showing a round homogeneously enhancing suprasellar mass similar in appearance to Case 1.

ning in the examination of suprasellar lesions[1–5] attest to the overall efficiency of the technique as a highly useful screening procedure for patients with neuro-ophthalmologic disorders. Our cases show that the density characteristics, contrast enhancement, and border configuration of suprasellar giant aneurysms, meningioma, and craniopharyngioma may be identical in the current state of computed tomography scanning. Thus, we believe further study is necessary in these patients.

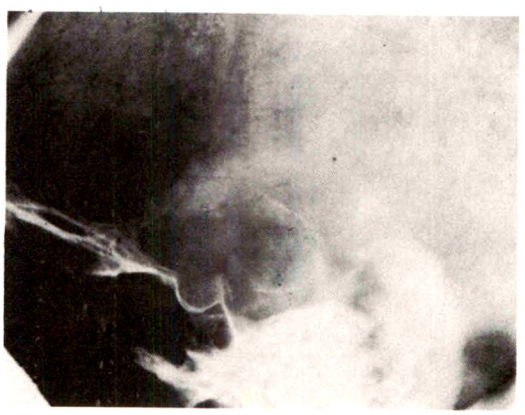

Fig. 3 (Kokoris, Rothman, and Wolintz). Case 3. Giant intracranial aneurysm (partially thrombosed and calcified). Lateral skull film shows curvilinear retro- and suprasellar calcification.

Noncalcified aneurysms generally have slightly higher density than brain, are sharply contoured, and enhance uniformly. These same characteristics may apply equally to noncalcified meningiomas. Suprasellar extension of chromophobe adenomas may have a similar configuration. Plain x-ray and geometric tomography generally show characteristic sella changes in the chromophobe adenomas and aid in the differentiation of pituitary tumors from purely suprasellar lesions.

On computed tomography calcified aneurysms share the same quality of well defined borders, but additionally show sharply circumscribed or punctate areas of high density reflecting the partial calci-

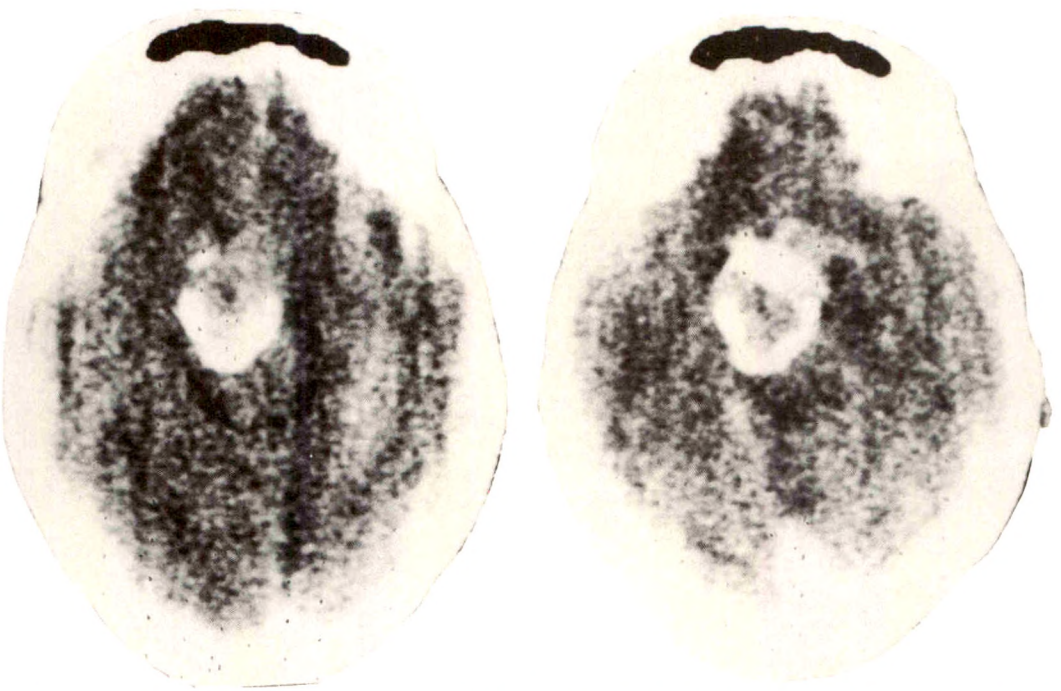

Fig. 4 (Kokoris, Rothman, and Wolintz). Case 3. Precontrast (left) and postcontrast (right) enhanced scans show a large partially calcified nonhomogeneously enhancing suprasellar mass. The nonenhancing central portion represents noncalcified thrombus.

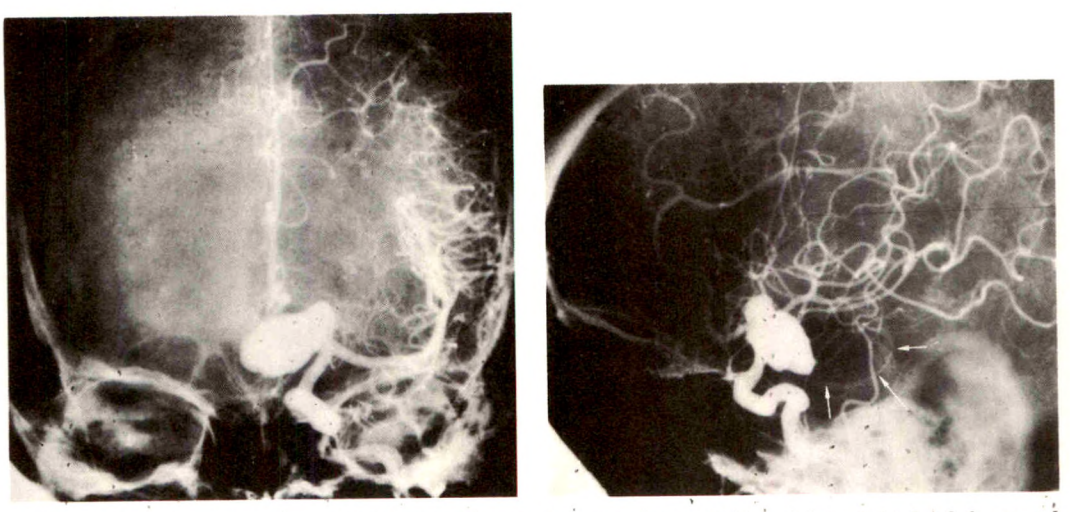

Fig. 5 (Kokoris, Rothman, and Wolintz). Case 3. Anteroposterior (left) and lateral (right) left carotid angiograms show the aneurysm arising from the carotid bifurcation and extending medially. The thrombosed posterior portion of the aneurysm is not filled with contrast and is outlined by the displaced anterior choroidal artery (arrows).

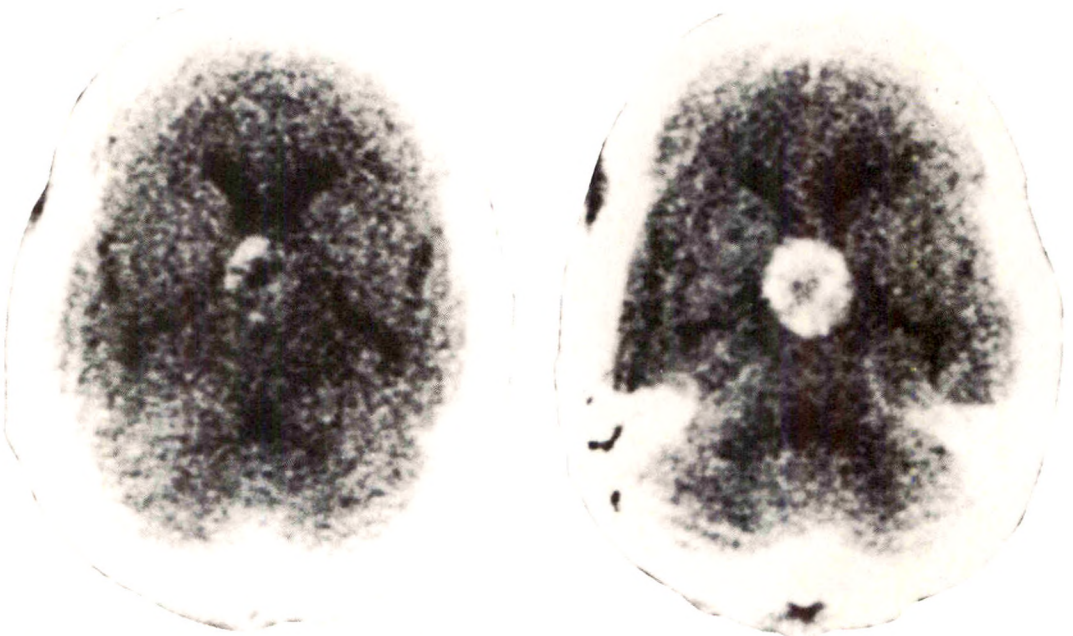

Fig. 6 (Kokoris, Rothman, and Wolintz). Case 4. Craniopharyngioma (partially calcified). Precontrast (left) and postcontrast (right) enhanced scans show a partially calcified nonhomogeneously enhancing round midline suprasellar mass.

fication of these lesions. Contrast enhancement is less homogeneous because of the presence of the calcification as well as the frequent occurrence of thrombotic material within all or a portion of the aneurysm. In a completely thrombosed aneurysm there may be no contrast enhancement or enhancement limited to the periphery, falsely suggesting a cystic mass.[6] Enhancement in the periphery is thought to represent the vasa vasorum of the aneurysm wall.[7]

The presence of calcification and nonhomogeneity of contrast enhancement thus simulates the appearance of craniopharyngioma on computed tomography.[4] Calcified meningiomas and pituitary adenomas may also share these characteristics.[4]

Angiography is the most reliable means of defining the presence of aneurysms, whereas computed tomography may be of considerable help in defining the full extent of those partially or completely thrombosed lesions as shown by Case 3. In view of the nonspecificity of computed tomography scanning, cerebral angiography remains an important means of examining patients with enhancing calcified or noncalcified suprasellar mass lesions.

Summary

We studied four cases in which the differentiation between a noncalcified suprasellar aneurysm and tuberculum meningioma, and a calcified suprasellar aneurysm and craniopharyngioma, could not be established by computed tomography scan alone. Cerebral angiography clearly showed both aneurysms.

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OPHTHALMIC MINIATURE

But I think that the influence which finally determined the character of my detective stories, and incidentally the character of John Thorndyke, operated when I was working at the Westminster Ophthalmic Hospital. There I used to take the patients into the dark room, examine their eyes with the ophthalmoscope, estimate the errors of refraction, and construct an experimental pair of spectacles to correct those errors. When a perfect correction had been arrived at, the formula for it was embodied in a prescription which was sent to the optician who made the permanent spectacles.

R. Austin Freeman,
Meet Dr. Thorndyke

MALIGNANT GLIOMAS OF THE OPTIC NERVE PATHWAYS

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Malignant gliomas of the optic nerve pathways are rare in adults,[1,2] and differ from benign optic gliomas that occur in childhood and are considered by some to be hamartomas with self-limiting growth and morbidity.[1,3,4]

Adult optic glioblastomas are aggressive, causing rapid visual deterioration and subsequent death. They are rarely diagnosed before craniotomy or autopsy.[1,2,5] Hoyt and associates[1] examined the clinical and pathologic nature of this tumor and defined a characteristic syndrome consisting of the following: (1) occurrence in middle-aged men; (2) initial signs and symptoms resembling optic neuritis; (3) blindness in two to four months; (4) death in six to nine months.

Recent reports indicate that this tumor can occur with visual loss in older individuals of either sex despite normal ophthalmologic and neuroradiologic results.[2,5] We describe herein five cases of malignant optic pathway gliomas, from a single institution, all diagnosed before death. We compared the clinical courses and pathologic features with those in other series.

MATERIAL AND METHODS

Biopsy specimens from four cases were examined. In three patients (Cases 2-4), fragments for paraffin embedding techniques were fixed in buffered 10% formalin; sections were stained with hematoxylin and eosin, and studied by light microscopy.

In one patient (Case 5) the biopsy specimen from the left optic nerve was fixed in Karnovsky (4% paraformaldyhyde and 2% glutaraldehyde in Sorenson's buffer) and embedded in plastic for ultrastructural studies. Plastic-embedded sections (1μ) stained with toluidine blue were studied by light microscopy. Ultrathin sections were mounted in 240-hole copper grids, stained with lead citrate and uranyl acetate, and observed in a Philips 200 electron microscope.

CASE REPORTS

Case 1—A 69-year-old woman complained of bilaterally blurred vision in December 1970. Results of ophthalmologic examination were normal except for the visual acuity, which was R.E.: hand motions and L.E.: 6/60 (20/200). The left eye was amblyopic. Skull x-rays and brain scan were normal. The patient was treated with systemic prednisone. One month later, she was referred for examination. Examination revealed visual acuity of R.E.: hand motions and L.E.: 6/60 (20/200) with marked dyschromatopsia. A right inferior, total altitudinal fixation defect was present as was a left inferior, dense paracentral scotoma. A right afferent pupillary defect was present. The fundus and optic disks appeared normal bilaterally. A tentative diagnosis of right ischemic optic neuritis was made. Two months later, the right eye was amaurotic and visual acuity in the left eye remained 6/60 (20/200). Optic disks and fundi remained normal. A corrected sedimentation rate was 15 mm/hr. X-rays of the skull and optic foramen were normal. The sella turcica was somewhat enlarged and demineralized, suggesting an infrasellar mass. Bilateral carotid angiograms were normal. Pneumoencephalography showed an extrinsic impression of the anterior right third ventricle, suggesting a small suprasellar mass.

Exploratory craniotomy revealed a smooth enlargement and a red-gray discoloration of the optic nerves and chiasm. Histologic examination of a biopsy specimen confirmed the operative impres-

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sion of a malignant astrocytoma. There was no evidence for extension beyond the optic nerve pathways.

Postoperatively, the chiasmal region was irradiated (5,000 rads during five weeks). Vision continued to deteriorate. She was totally blind eight months after her initial examination and died a few months later. Permission for autopsy was not granted. The histopathologic specimen was not available for examination.

Case 2—A 64-year-old woman was referred for examination in March 1975 for progressive bilateral visual dysfunction attributed to venous stasis retinopathy. Two weeks before referral, examination revealed decreased vision and a hemorrhagic papillopathy in the left eye. Skull x-rays, brain scan, electroencephalogram, and lumbar puncture were reported as normal.

Our initial examination revealed visual acuity was R.E.: 6/60 (20/200) and L.E.: light perception. The pupils were sluggishly reactive. Ophthalmoscopic examination revealed bilateral disk edema and an appearance similar to venous stasis retinopathy. Skull x-rays and bilateral carotid arteriograms were normal. Pneumoencephalography revealed blunting of the anterior recess of the third ventricle by a suprasellar mass.

Craniotomy revealed swelling and discoloration of the optic nerves and chiasm with extension to the adjacent hypothalmus. A biopsy was performed.

Histopathologic examination revealed a highly cellular, malignant neoplasm, composed of atypical, bizarre astrocytes with giant cells and occasionally spindle-shaped and multi-polar astrocytes with pleomorphic and hyperchromatic nuclei. Disrupted myelin sheaths and axons were present within the neoplastic elements (Fig. 1). The diagnosis of malignant astrocytoma was made.

Postoperatively, she was treated with radiation therapy. She was totally blind one month after the onset of her visual symptoms. Dementia and lethargy followed and she died nine months after the onset of symptoms. Autopsy was not permitted.

Case 3—A 59-year-old man was first examined in March 1978 three weeks after the onset of bilateral blurred vision. No other ocular symptoms were noted. General health was excellent except for adult-onset diabetes mellitus which was well controlled with oral hypoglycemics.

Visual acuity on initial examination was R.E.: hand motions and L.E.: 6/60 (20/200) with marked dyschromatopsia. Visual fields revealed bilateral inferior altitudinal defects with loss of fixation. An afferent pupillary defect was present in the right eye. Motility was normal. The optic disks appeared normal. The arterioles were slightly attenuated; the fundi were otherwise unremarkable.

Skull x-rays were normal. Computed axial tomography revealed an enhancing mass in the sellar region. This was confirmed by carotid angiography. The mass was believed to be a meningioma. At craniotomy, the optic nerves and chiasm appeared enlarged and elevated. Examination of a biopsy specimen from the region of the chiasm revealed a moderately cellular tumor with numerous foci of mucoid degeneration with frequent hyperchromatic, bizarre, malignant glial cells (Fig. 2).

The patient was blind four weeks after the onset of his visual symptoms and he died six months later. Permission for autopsy was not granted.

Case 4—A 64-year-old man was referred to us in April 1978 with a three-week history of pain and loss of vision in the right eye. Neuro-ophthalmologic examination revealed an amaurotic right eye with an afferent pupillary defect, 3 mm of proptosis, and a right lateral rectus palsy. Visual acuity was 6/12 (20/40) in the left eye with mild dyschromatopsia. The left visual field was normal. Ophthalmoscopic examination of the right eye revealed a markedly edematous disk and hemorrhagic retinopathy with attenuation of the arterioles. The left fundus was unremarkable. Computed axial tomography re-

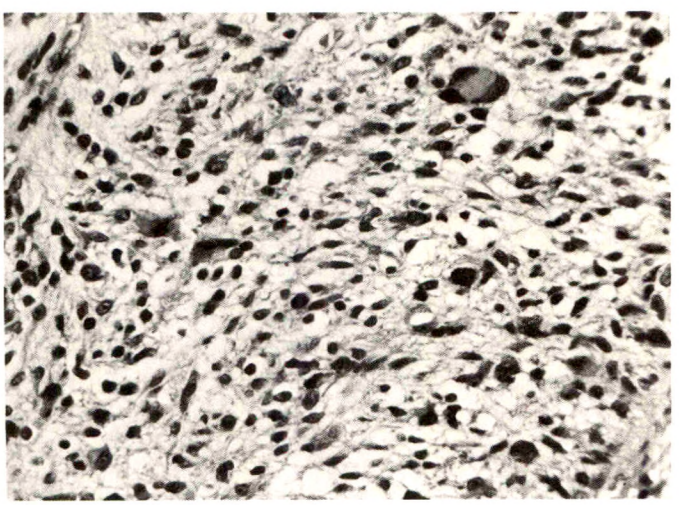

Fig. 1 (Spoor and associates). Case 2. Photomicrograph showing a poorly differentiated glial neoplasm with numerous malignant multinucleated giant cells. Atypism and pleomorphism of glial elements are obvious (hematoxylin and eosin, ×250).

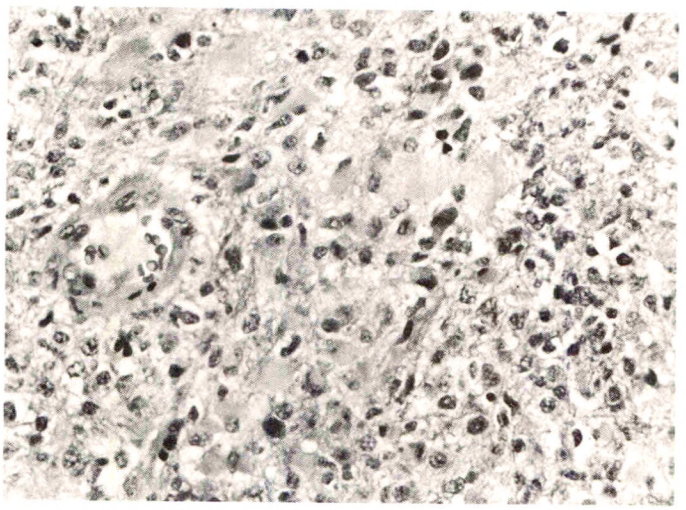

Fig. 2 (Spoor and associates). Case 3. Photomicrograph showing an anaplastic astrocytoma containing numerous foci of mucoid degeneration. Frequent hyperchromatic, bizarre malignant glial cells are seen (hematoxylin and eosin, ×250).

vealed an enlarged right optic nerve. Tomograms of the optic foramina were normal. Three weeks later, visual acuity in the left eye decreased to 6/15 (20/50) and the visual fields revealed both a peripheral and central superior temporal defect.

A fine needle aspiration biopsy of the enlarged right optic nerve under computed axial tomography visualization disclosed cytologic evidence of a malignant astrocytoma. The right orbit was subsequently explored through a medial orbitotomy. The optic nerve was markedly enlarged and violaceously discolored. A biopsy was performed.

Histopathologic examination showed a scantily cellular neoplasm composed of sparsely located spindle-shaped, astrocytic cells with irregular, mild pleomorphism, and moderate hyperplasia of blood vessels (Fig. 3). No Rosenthal fibers were evident.

Postoperatively, the left optic nerve and chiasm were irradiated and the patient was treated with systemic prednisone. Visual acuity in the left eye improved initially to 6/9 (20/30). Subsequently, visual acuity and visual field rapidly deteriorated in the left eye and the left optic nerve became atrophic. Total occlusion of the retinal arterioles and venules developed in the right eye, followed by rubeosis of the iris and marked increase of intraocular pressure, necessitating cyclocryotherapy for relief of pain.

Six months after the onset of visual symptoms, he was totally blind. Seizures, dementia, and hyperglycemia developed and death occurred three months later. Permission for autopsy was not granted.

Case 5—A 60-year-old woman was referred to us in August 1978 with a three-week history of rapidly decreasing vision and bifrontal headaches. Medical history revealed mild hypertension and adult onset diabetes mellitus. Results of neurologic examination, including an electroencephalogram and computed axial tomography before referral were normal.

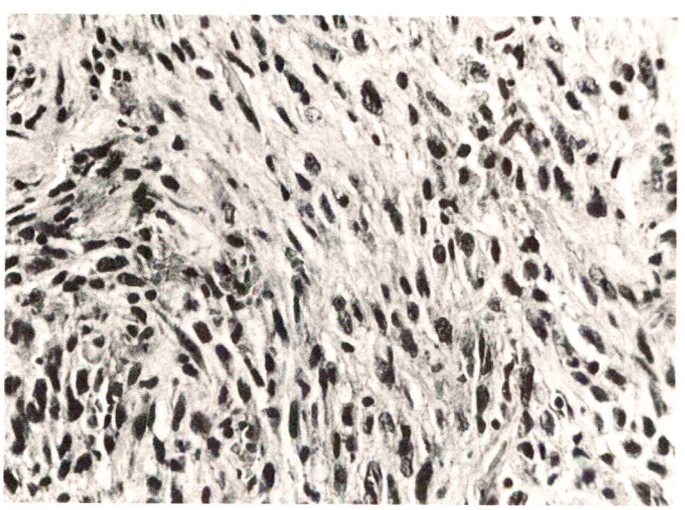

Fig. 3 (Spoor and associates). Case 4. This tumor is composed of elongated, spindle-shaped hyperchromatic astrocytes. Relative abundant intercellular glial processes are seen within neoplastic elements (hematoxylin and eosin, ×250).

Initial ophthalmologic examination revealed visual acuity of counting fingers in both eyes and marked dyschromatopsia. There was a dense central scotoma with peripheral constriction in the right eye and a total inferior altitudinal defect with loss of central fixation in the left eye. Pupils were equal but sluggishly reactive. Results of slit-lamp examination and intraocular pressures were normal as was ocular motility.

Ophthalmoscopic examination revealed minimal background diabetic retinopathy and normal optic disks in both eyes. The sedimentation rate was 49 mm. Temporal artery biopsy specimens were normal. Skull x-rays and computed axial tomography were normal. A trial of systemic prednisone relieved the headaches and it subjectively improved vision. Subsequently, visual acuity and visual fields progressively deteriorated. Minimal pallor of the disks became evident.

An electroretinogram was normal. Repeat enhanced computed axial tomography (American Science and Engineering 512 matrix) with coronal sectioning was normal. Visually evoked response was markedly diminished bilaterally. Polytomography of the optic foramina and sella turcica was also normal. Bilateral carotid angiography, metrizamide cisternography, and pneumoencephalography with midline tomography were also normal.

Visual acuity and visual fields continued to deteriorate and pupillary responses became amaurotic. The chiasmal and prechiasmal regions were explored through a right frontal craniotomy. At craniotomy, the optic nerves and chiasm appeared grossly normal, although the left optic nerve was questionably distended. A biopsy specimen was taken of the left optic nerve. The specimen was characteristic of a highly cellular malignant neoplasm composed of atypical, bizarre astrocytes with disrupted myelin sheaths and axons within neoplastic elements (Fig. 4).

Postoperative irradiation treatment was given. The patient was blind two months after her initial visual symptoms and she died four months later.

Discussion

Since Hoyt and associates[1] defined the syndrome of malignant glioma of the optic nerve pathway, six additional cases have been reported.[2,5–7] In our five cases as in previous cases, the initial diagnoses were erroneous. All five cases were diagnosed by surgical exploration; four by craniotomy and one by fine needle aspiration biopsy of the enlarged optic nerve under computed axial tomography.[8] This diagnosis was subsequently confirmed by open biopsy of the optic nerve via a medial orbitotomy.

After reviewing our cases and those previously reported, we found that malignant optic gliomas do not appear to comprise a remarkably uniform neuro-ophthalmologic entity as previously reported.[1]

Our patients ranged in age from 59 to 65 years (average, 63.4 years). Three were women and two were men. These data combined with those previously published[1,2,5–7,9,10] gave a total of 26 patients whose ages ranged from 22 to 79 years (average, 51.9 years). Of these 26, 15 were men and 11 were women. Our series did

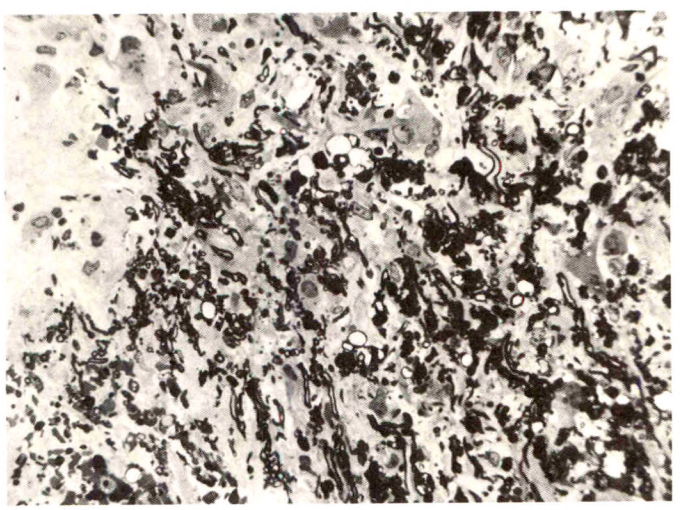

Fig. 4 (Spoor and associates). Case 5. Photomicrograph revealing numerous disrupted myelin sheath intermingling with bizarre, atypical astrocytes. Plastic-embedded tissue (toluidine blue, ×250).

not show the marked statistical tendency for middle-aged men, as previously described.[1]

Visual loss in our patients was rapid and unrelenting; with blindness ensuing in a matter of months (average, 3.6; range, one to eight months) and death following shortly thereafter. This sequence of events and rapid course is similar to that described by others.[1,2,5–7,9,10]

Our patients all had blurred or dimming vision as the initial symptom, bilaterally in four of the five. Bilateral involvement has been reported by others,[2,5] although initial monocular involvement has been described as characteristic.[1,7,9,10] As in other reports, periorbital pain was a common early symptom in our patients. Table 1 shows the initial ocular findings in our patients and those previously reported.[1,2,5–7,9,10] There is an equal incidence of unilateral and bilateral visual dysfunction as the initial symptom. It was also evident that optic disk edema was present on initial ophthalmologic examination in slightly over one half of these patients. Three of our patients and all of Harper and Stewart-Wynne's[5] patients had nearly normal appearing disks and fundi throughout their illness.

The failure of these patients to develop disk edema and venous stasis probably results from a tumor located more centrally in the anterior visual pathways. Our three patients with normal fundi (Cases 1, 3, and 5) all had bilateral severe visual dysfunction and bilateral inferior altitudinal visual field defects with loss of central vision.

TABLE 1

INITIAL OCULAR FINDINGS IN 18 PATIENTS WITH MALIGNANT GLIOMAS OF THE AFFERENT VISUAL PATHWAY

Initial Symptom	No.	Percent
Decreased Vision	18	100
Unilateral	9	50
Bilateral	9	50
Disk		
Edema	10	55.5
Normal or mild atrophy	8	44.5

Table 2 relates the visual field defects found in 13 patients to the ophthalmoscopic appearance of their optic disks. Those patients with optic disk edema in one eye and a normal appearing contralateral disk, had dense central defects in the eye with the edematous disk, and a contralateral temporal hemianopia, progressing to involve central visual acuity. Those patients with similar defects and bilaterally normal optic disks probably had tumors originating more centrally in the optic nerve or chiasm.

Two patients (Harper and Steward-Wynne's[5] Cases 2 and 3) with homonymous hemianopia had extensive involvement of their cerebral hemispheres with tumor and appropriate neurologic deficits. Their fundi were normal. Autopsy showed infiltration of the optic tract, chiasm, and right cerebral hemispheres.

One of our patients (Case 4), had extensive ocular and orbital involvement; proptosis, conjunctival chemosis, ophthalmoplegia, optic disk swelling, central retinal vein occlusion, ischemic signs of the anterior segment, and hemorrhagic glaucoma. At orbitotomy, the intraorbital optic nerve was enlarged, violaceously discolored, and involved with tumor. A similar case has been described.[7]

Table 3 summarizes ocular and orbital complications reported in 26 malignant gliomas of the optic nerve pathways.[1,2,5–7,9,10] We agree with a previous review[1] that orbital and ocular complications are not frequent and result from invasion of tumor into the orbit. Only one of our patients (Case 4) had such involvement. He also had partial ophthalmoplegia as did the case reported by Hamilton and associates.[7]

The initial symptoms in all of our patients were ocular. Neurologic complica-

TABLE 2

INITIAL VISUAL FIELDS AND OPTIC DISKS IN 13 PATIENTS WITH MALIGNANT GLIOMAS OF THE AFFERENT VISUAL PATHWAY

Visual Field Defect	No.	Percent	Disk Appearance
Inferior altitudinal in both eyes	3	23.1	Normal, both eyes
Central scotoma Contralateral temporal	2	15.4	Normal, both eyes
Homonymous hemianopia	2	15.4	Normal, both eyes
Central scotoma Contralateral temporal	6	46.1	Edema and stasis Normal (contralateral)

tions occurred late, were mild in the early stages in some (Cases 1, 3, and 5), and marked in others (Cases 2 and 4). The predominance of ocular symptoms with the late occurrence of neurologic symptoms suggests that these tumors originated in the optic nerve pathways.

Adult-onset diabetes mellitus was present before the development of ocular symptoms in two of our patients (Cases 3 and 5). The patient in Case 4 developed marked hyperglycemia before death with marked personality changes.

Skull and optic foramina x-rays were not abnormal in any of our patients. In one case (Case 1), the sella turcica was thought to be enlarged, indicating a possible intrasellar mass. Carotid angiography showed an enhancing sellar mass in Case 3, but was normal in three others. Computed axial tomography was performed on three patients and was abnormal in two. The computed axial tomography in Case 4 showed a swollen optic nerve and a biopsy specimen was taken, sparing the patient a craniotomy. An enhancing sellar mass was shown in Case 3. In Case 5, computed axial tomography combined with metrizamide cisternography was normal. This same patient had relatively normal appearing visual pathways at craniotomy, the diagnosis was made from a biopsy specimen of a questionably distended left optic nerve. Pneumoencephalography revealed subtle abnormalities in Cases 1 and 2, and was normal in Case 5.

TABLE 3

ORBITAL AND OCULAR COMPLICATIONS IN 26 PATIENTS WITH MALIGNANT GLIOMAS OF THE AFFERENT VISUAL PATHWAY

Complication	No.	Percent
Proptosis	6	23
Edema/chemosis	3	11.5
Ophthalmoplegia	7	26.9
Glaucoma (hemorrhagic)	3	11.5

Table 4 summarizes the diagnostic value of various neurologic procedures in 11 recently reported cases[1,2,5–7] and five of our own. Computed axial tomography appears to be a good diagnostic modality; but has not been used often in these cases. It revealed abnormalities in two of the three cases described previously. In one other (Harper and Stewart-Wynne's[5] Case 2) a large enhancing mass was indicated in the right cerebral hemisphere.

Cerebral angiography and pneumoencephalography yielded inconclusive results in approximately one half of the cases. Plain skull x-rays of the optic foramina and chiasm were generally unrevealing.

Exploratory craniotomy and biopsy were necessary to make a diagnosis in four of our five cases. In Case 4 the diagnosis was made by fine needle aspira-

TABLE 4

NEURORADIOLOGIC EVALUATION IN 16 PATIENTS WITH MALIGNANT GLIOMAS OF THE AFFERENT VISUAL PATHWAY

Procedure	Percent Abnormal	No. of Patients
X-rays		
Skull series	6.2	16
Optic canals	16.6	12
Sella turcica	15.4	13
Computed axial tomography	75	4
Angiography	41.6	12
Pneumoencephalogram	54.5	11

tion biopsy of an enlarged optic nerve; this was subsequently confirmed by open biopsy through a medial orbitotomy. Our experience supports the premise that malignant gliomas may originate in either optic nerve, tract, or chiasm and extend proximally and distally.[1,7] Patients with gliomas of proximal origin have bilateral visual dysfunction and normal appearing fundi (Cases 1, 3, and 5). A patient with a tumor originating more distally in an optic nerve may have unilateral visual dysfunction, ophthalmoscopic signs of optic disk edema, and venous stasis. As growth proceeds proximally, a contralateral superior temporal hemianopia develops and the inferior nasal crossing fibers are involved in the proximal optic nerve. With further growth and extension into the chiasm, subsequent loss of central visual acuity ensues. The optic disk will appear normal or slightly atrophic. However, if the predominent growth extends distally along the contralateral optic nerve, disk edema and venous stasis will accompany contralateral visual dysfunction. A patient with a tumor originating more proximally and extending in a predominantly posterior direction, may have hemiparesis and hypothalamic symptoms preceding visual loss (Hoyt and associates,[1] Case 3) or accompanying it (Harper and Stewart-Wynne's[5] Cases 2 and 3).

We believe that the method of exploration and diagnosis depends on the location of the tumor and the clinician's judgment. In a patient with a distally located tumor and rapid, unilateral, progressive visual loss and ophthalmoscopic signs of disk swelling and venous stasis, a diagnosis may be made either by fine needle aspiration biopsy[8] or orbitotomy (medial or lateral). Patients with more proximally located tumors and progressive, bilateral visual loss, and negative findings of ophthalmologic and neuroradiologic examinations should undergo exploratory craniotomy with biopsy of the optic nerve.

All five of our patients were treated with a course of radiation therapy. It was not effective in any patients. As in other reports,[1,2,5] the tumor progressed rapidly and no known treatment has had any beneficial effect.

Permission for autopsy was not granted in any of our cases. Histologic diagnosis was made from biopsy specimens obtained at craniotomy or orbitotomy. Table 5 compares the histopathologic features observed in four of our five biopsy specimens (Cases 2-5). The specimen from Case 1 was unavailable for examination.

Microscopic features of severe malignancy showing pleomorphic, atypical, and mitotically active astrocytes were evident in Cases 2, 3, and 5 (Figs. 1, 2, and 4). One specimen (Case 4) (Fig. 3) ap-

TABLE 5

HISTOPATHOLOGIC FEATURES IN FOUR CASES OF MALIGNANT GLIOMAS OF THE AFFERENT VISUAL PATHWAY

Case No.	Histologic Features	Histologic Diagnosis
2	Densely cellular; marked atypia; pleomorphism, hyperchromatism; giant cells; rare mitosis; and vascular and endothelial proliferation	Glioblastoma multiforme
3	Less cellular; modest atypism; mild cellular pleomorphorism; foci of mucoid degeneration; hyperplasia of blood vessels, severe	Anaplastic astrocytoma
4	Densely cellular, elongated, spindle-shaped astrocytes; modest atypism; mild pleomorphism hyperchromatism; rare mitosis	Well-differentiated astrocytoma
5	Myelin sheaths separated by bizarre, atypical, and pleomorphic astrocytes	Glioblastoma multiforme

peared to be a well-differentiated astrocytoma. Biopsy specimens of a well-differentiated glial neoplasm without significant atypical astrocytes, obtained from a clinically aggressive lesion, have been previously described[1] and the aggressive nature of the tumor subsequently confirmed at autopsy.[1] Extensive vascular and endothelial proliferation, as well as disruption of myelin sheaths and axons, were also noted and have been described by others.[1,7]

We also believe that adult-onset optic gliomas are acquired and originate primarily in the optic nerve pathways, although this premise cannot be established by histopathologic evidence alone.[1] Supporting this premise, Hoyt and associates[1] stated that initial symptoms occur during adulthood and originate in the anterior visual pathways.

Initially, all our patients had symptoms of visual dysfunction referable to the optic nerves or chiasm as the sole manifestation of their tumor. Additionally, neurosurgical exploration in two patients (Cases 1 and 5) revealed abnormalities confined to the optic nerve or chiasm and no evidence for extension to adjacent structures.

SUMMARY

We compared the clinical course and histopathologic findings in five patients with malignant gliomas originating from the optic nerve pathways with those in previously reported cases to elucidate further the clinical features of this tumor and facilitate future diagnoses. Patients with malignant optic nerve pathway gliomas had unilateral or bilateral visual dysfunction, which was often accompanied by periorbital discomfort in an otherwise asymptomatic adult. Regardless of origin, the clinical course invariably was bilateral blindness rapidly followed by death. Occasionally, the diagnosis was made preoperatively and was confirmed by surgical exploration and biopsy.

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THE CEREBRO-OCULO-FACIO-SKELETAL SYNDROME

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We report herein a case of the cerebro-oculo-facio-skeletal syndrome and review its features, which include microphthalmia, cataract, and blepharophimosis. This is an important syndrome to recognize because of its ophthalmologic features, recessive inheritance, and generally poor prognosis. The cerebro-oculo-facio-skeletal syndrome should be considered in the differential diagnosis of congenital cataract.

CASE REPORT

The patient was first seen at 3½ months of age by the pediatric service where he had been admitted because of failure to thrive and microcephaly. He had difficulty in feeding. At birth, he weighed 2700 g and was 47.5 cm in length, the product of an estimated 32-week gestation. His 28-year-old mother (gravida 3, para 2) and 35-year-old father are first cousins once removed (Fig. 1).

Physical examination showed his length to be 56 cm, his weight 3,700 g, and his head circumference was 34 cm. There was temporal narrowing and fine sparse hair. The ears were 4 cm in length with a small lobar pit on the left ear.

There was a high nasal root and short palpebral fissures with a slight upward slant. The eyes were deep set and appeared small. The corneas were clear, the horizontal diameters were R.E.: 8 mm, and L.E.: 9 mm. The pupils were equal in size and reacted to light. The irides dilated poorly with tropicamide (Mydriacyl). Cataracts were seen bilaterally; they were most dense centrally but involved the entire lens. The fundi were not well visualized but the optic nerves were described as normal.

The thorax had an increased anteroposterior diameter with kyphosis of the spine. The genitalia were normal. The upper extremities showed normal extension but the hips and knees showed moderate contractures. The left hand had a single palmar crease. Neurologic examination showed poor head control and a weak grasp. Moro's reflex was present.

Chromosome analysis revealed a normal 46 XY karyotype. Serum titers for herpes simplex, cytomegalic inclusion disease, and toxoplasmosis were negative. Herpes and cytomegalic titers of cerebrospinal fluid were also negative. Amino acid screen of the urine and electroencephalogram were normal. Skull x-rays were normal without calcifications, bone age was that of a newborn, and esophagram revealed a small hiatal hernia. Computed axial tomography of the brain was normal.

The patient was seen in consultation by the genetics service and because of the distinctive dysmorphic features in association with a consanguineous parentage, the diagnosis of cerebro-oculo-facio-skeletal syndrome was made.

The patient was seen again at 24 months of age in the genetics clinic (Fig. 2). He was still having difficulty feeding, but had learned to turn over at 1

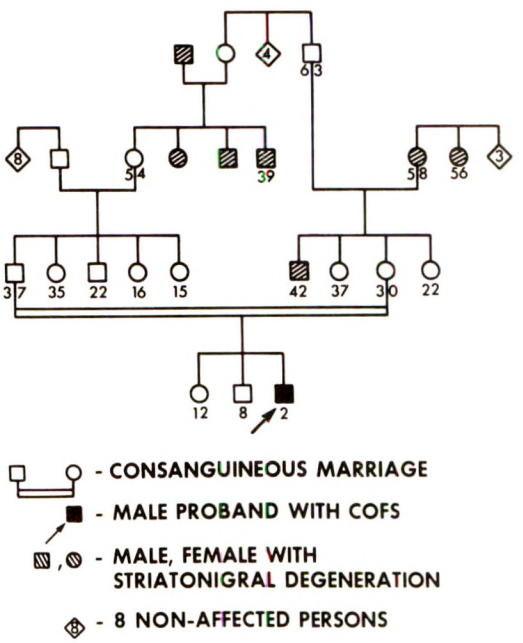

Fig. 1 (Grizzard, O'Donnell, and Carey). Pedigree of patient with cerebro-oculo-facio-skeletal (COFS) syndrome.

From the Departments of Ophthalmology (Drs. Grizzard and O'Donnell) and Pediatrics, Division of Genetics (Dr. Carey), University of California, San Francisco, California. This study was supported in part by a Basil O'Connor Award from the National Foundation—March of Dimes (Dr. O'Donnell).

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Fig. 2 (Grizzard, O'Donnell, and Carey). Patient with cerebro-oculo-facio-skeletal syndrome. Note deep set eyes and prominent nasal bridge.

year and had learned to sit at 1½ years. He could say a few words in Portuguese but could not walk. Physical examination now revealed a length of 61 cm and a weight of 3,900 g. Head circumference was 36 cm. He had searching nystagmus but appeared to see bright light and large objects. Palpebral fissures were 1.5 cm in length. Corneal diameters were unchanged. Biomicroscopic examination showed a superficial corneal opacity at the inferior corneoscleral limbus in both eyes. The lenses were opaque with a dense white opacity centrally involving the fetal nucleus. The fundi could not be seen.

Discussion

In 1971, Lowrey and associates[1] reported a case of two siblings of nonconsanguineous, unaffected parents who had a new syndrome of cataracts, microcephaly, and limited joint mobility. Pena and Shokeir[2] in 1974 reported ten cases which had many similiar features and called it the cerebro-oculo-facio-skeletal syndrome. They described the salient features of this syndrome as severe microcephaly, microphthalmus, cataracts, blepharophimosis, apparently large pinna, overlapping upper lip, long philtrun, micrognathia, flexure contractures, kyphosis, camptodactyly, rocker-bottom feet, and a longitudinal plantar groove. Other features were widely set nipples, failure to thrive, developmental retardation, feeding difficulties, and simian creases (Table).

Renal anomalies were present in one of the ten patients reported by Pena and Shokeir.[2] Preus, Kaplan, and Kirkham[3] found them in two patients with cerebro-oculo-facio-skeletal syndrome. Renal anomalies may cause decreased production of amniotic fluid, leading to oligohydramnios and the deforming features of Potter's syndrome which may obscure the diagnosis of cerebro-oculo-facio-skeletal syndrome.[4–6]

Most of the patients with cerebro-oculo-facio-skeletal syndrome have not survived past 3 years of age and all have been severely retarded. Two of the four cases reported by Scott-Emuakpor, Heffelfinger, and Higgins[7] lived into the second decade, but were institutionalized and weighed less than 6,000 g. This family may represent a milder form or a different syndrome, but in our opinion is sufficiently similar to warrant inclusion until biochemical or histologic markers are identified. A paternal sibling of this family was affected with a dominantly inherited amyotrophic lateral sclerosis. Our patient's maternal grandmother and pa-

TABLE

FEATURES OF CEREBRO-OCULO-FACIO-SKELETAL SYNDROME*

	Lowery and associates[1] 1971	Pena and Shokeir[2] 1974	Preus and Fraser[15] 1974	Lurie and associates[16] 1976	Kaplan, Preus, and Kirkham[3] 1977	Heffelfinger, Scott-Emuakpor, and Higgins[7] 1977	Present Case 1979	Total
Author's diagnosis	New syndrome	COFS	COFS	COFS	COFS	New syndrome	COFS	
No. of cases	2	10	1	1	2	4	1	21
No. of families	1	3	1	1	2	1	1	10
Consanguineous families	0	1	1	1	0	0	1	4
General features								
Low birth weight	2	7/7†	1	1	2	4	1	18/18
Failure to thrive	2	10	1	NA	2	4	1	20/20
Difficulty feeding	2	10	NA	NA	1/1†	NA	1	14/14
Widely set nipples	NA	5/7†	0	1	0	NA	1	7/12
Renal abnormalities	0/1†	1	NA	1	2	NA	1	5/15
Undescended testes	1/1†	0/6†	Female	Female	1/1†	1/1†	0	3/10
Severely retarded	2	10	Died at 6 days	Died at 7 days	Died at 1 and 27 days	4	1	17/17
Cerebral								
Agenesis of corpus colosum	0/1†	NA	NA	1	NA	2/2†	0	3/5
Microcephaly for age	2	10	1	1	1/1†	4	1	20/20
Sparse hair	2	Hirsute	0	0	NA	0/2†	1	3/17
Ocular								
Microphthalmia	1/1†	8/8†	1	1	1	NA	1	13/14
Cataracts	2	4/8†	1	1	1	4	1	14/19
Blepharophimosis	2	6/7†	1	1	1	NA	1	12/14

(Table continued on following page)

TABLE (*Continued*)

FEATURES OF CEREBRO-OCULO-FACIO-SKELETAL SYNDROME*

Facial								
High or prominent nasal bridge	1/1†	7/7†	1	1	2	NA	1	13/13
Overlapping upper lip	NA	7/7†	1	1	1	NA	1	11/12
Micrognathia	NA	8/8†	0	0	2	NA	1	11/13
Skeletal								
Hip dysplasia	1	3/7†	1	0	1	4	0	10/18
Kyphosis/scoliosis	2	7/8†	1	0	1	4	1	16/19
Rocker bottom feet	NA	6/9†	1	1	1	2/2†	1	12/16
Longitudinal foot groove	NA	6/7†	0	NA	1	NA	1	8/11
Limb contractures	2	7/9†	1	1	2	4	1	18/20
Camptodactyly	NA	9/9†	1	1	2	NA	0	13/14
Laboratory examination								
Normal chromosomes (Abnormality)	2	9 47xxx	1	NA	1 "Unusual D chromosome"	1/1	1	15/17
Normal urine screen	2	10	NA	NA	NA	3/3†	1	16/16

*NA designates information not available; COFS, cerebro-oculo-facio-skeletal syndrome.
†Data available or applicable only in some of cases reported.

ternal great-grandfather are affected with dominantly inherited striatonigral degeneration, which has a variable onset between 16 and 65 years of age.[8,9] The paternal grandmother is reaching the age (54 years) at which it is unlikely she will be affected (Fig. 1). The association between cerebro-oculo-facio-skeletal syndrome and dominantly inherited neurologic degenerative disease in this family from the Azores may be coincidental. The consanguinity comes from the maternal grandfather and paternal great-grandmother who are siblings but are not affected with striatonigral degeneration. The possibility of a doubly consanguineous pedigree must be considered because striatonigral degeneration is a rare disease limited to patients from the Azores.

Other disorders in the differential diagnosis are Cockayne's syndrome,[10,11] Seckel's syndrome,[12,13] and Potter's anomaly.[4–6] Our patient appears similar to patients with Cockayne's syndrome because of microcephaly, deep-set eyes, sparse subcutaneous tissue, and joint contractures. However, because of his small size at birth, marked failure to grow rather than arrest of normal growth, cataracts, blepharophimosis, marked early feeding difficulty, and absence of skin sensitivity to light, he fits better the description of the cerebro-oculo-facio-skeletal syndrome.

Similarities also exist between our patient and patients with Seckel's syndrome. The prenatal onset of growth deficiency, developmental delay, sparse hair, and prominent bridge of the nose are typical of Seckel's bird-headed dwarfs. However, the ocular feature of microphthalmia, cataracts, and blepharophimosis differentiate our patient from those of Seckel who stressed that the eyes of his patients seemed exempt from "dwarfish organ size."

In 1946, Potter[4] described the facial characteristics associated with bilateral renal agenesis. These features were prominent epicanthal folds, a flattened nose, a receding chin, and low-set ears with little cartilage. Other features were lung hypoplasia, limb positioning defects, and fetal growth deficiency. Thomas and Smith[6] have described patients with oligohydramnios and similar facial features but without renal agenesis and have postulated that the findings of Potter's syndrome are secondary effects of oligohydramnios.

Only one of 50 cases reported by Potter[5] had microphthalmia. The case of Potter's syndrome with microphthalmia and cataract reported by Brownstein, Kirkham, and Kalousek[14] was later reported by Preus, Kaplan, and Kirkham[3] as cerebro-oculo-facio-skeletal syndrome associated with bilateral renal agenesis. The pathologic findings reported by Brownstein, Kirkham, and Kalousek[14] include absence of keratocytes in the inner central corneal stroma, cataract with retention of cell nuclei in the lens nucleus, hypoplasia of the ganglion cells and nerve fiber layer of the retina, and absence of nerve bundles in the optic nerve.

Our family, and three of the other nine families reveiwed, have been consanguineous.[1–3,7,15,16] The cerebro-oculo-facio-skeletal syndrome would appear to be autosomal recessive and parents should be counseled accordingly.

Our patient is showing severe developmental retardation. Our decision not to do cataract surgery might be subject to reassessment, but currently the parents are not interested in surgical intervention.

Summary

A 3½-month-old boy with the cerebro-oculo-facio-skeletal syndrome had low birth weight, microcephaly, microphthalmia, cataracts, blepharophimosis, high nasal bridge, micrognathia, kyphosis, rocker-bottom feet, and a longitudinal foot groove. The product of a consanguineous parentage, he showed marked devel-

opmental retardation, suggesting abnormal recessive inheritance.

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UNIOCULAR CONGENITAL BLINDNESS AS A COMPLICATION OF MIDTRIMESTER AMNIOCENTESIS

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Jerusalem, Israel

The use of transabdominal midtrimester amniocentesis as a diagnostic means for prenatal evaluation of genetic and other congenital diseases has become, in recent years, a common procedure in medical practice. Amniocentesis performed in midtrimester has been assumed to be safe for both mother and fetus, as opposed to the known risks of this procedure at term. However, fetal ocular complications have been sporadically reported. In 1973, Cross and Maumenee[1] described a patient with ocular trauma that occurred during midtrimester amniocentesis. The findings of a hazy edematous cornea with signs of corneal perforation and a cystic structure, lined by stratified squamous epithelium, in the anterior chamber, were all attributed to trauma caused by the prenatal amniocentesis. In 1975, Fortin and Lemire[2] described a prenatal corneal perforation during full-term amniocentesis.

We describe herein a third case of an ocular trauma caused by amniocentesis. The findings appear to confirm the indirect evidence of Cross and Maumenee[1] that such a severe prenatal trauma to the eye is possible. Prenatal trauma should be considered in the differential diagnosis of congenital ocular conditions.

CASE REPORT

A 6-month-old girl was referred to us because of an abnormal left eye.

The girl was born as the fifth child to a healthy 42-year-old woman who had four other healthy children. The pregnancy and delivery were normal. In the 19th week of gestation a transabdominal amniocentesis was performed as a routine procedure because of the advanced maternal age.

The amniocentesis was performed as follows: Before the puncture, ultrasound scanning was performed for localization of placenta and fetus. Biparietal diameter was 4.80 cm. Immediately after the scan, while the pregnant woman was still lying on the bed, amniocentesis was performed. The first 2 ml of amniotic fluid was stained with blood; an additional 30 ml was clear. After this procedure the fetal heart rate was normal, and the mother did not have any complaints. Examination of the blood-stained amniotic fluid revealed fetal blood.

The routine examination on the first day of life revealed a normal healthy baby except for a small and cloudy left eye. At age 6 months, examination was performed with the baby under anesthesia. The right eye was normal. The left orbit was slightly shallow. The left upper eyelid had a shallow elongated small coloboma, medial to the center (Fig. 1). The eye was microphthalmic. Axial length by ultrasound A-mode was 19 mm in the right eye and 14 mm in the left eye. The left eye was soft. The corneal diameter was 10.5 mm in the right eye and 9 mm in the left eye. The cornea was hazy and edematous (Fig. 2). We noted a vascularized leukoma about 2 mm medial to the center.

DISCUSSION

The findings of a congenital coloboma of the eyelid together with signs of an

Fig. 1 (Merin and Beyth). The eyelids of the left eye. Note the shallow coloboma of the upper eyelid (between arrows).

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Fig. 2 (Merin and Beyth). The left cornea, hazy and 9.5 mm in diameter. The eye was microphthalmic and a vascularized leukoma corneae (arrow) involved all layers of the cornea.

"old" corneal perforation in the presence of an undeveloped left eye indicate an intrauterine injury to this eye. This combination of findings looked different from any known or previously described congenital anomaly or chromosomal aberration. The appearance of an injury to both the eyelid and cornea indicates that the trauma occurred before the separation of the eyelids and before the development of a free eyelid margin—between the beginning of the third gestational month and the end of the fifth month.[3] This coincides with an injury caused by the amniocentesis in the 19th gestational week. Fetal blood, found in the amniocentesis fluid in this case, indicates that either the fetus or its placenta was injured.

The similarity of the corneal findings in the present case and in the patient of Cross and Maumenee[1] is remarkable. Signs of an old perforation in a hazy cornea may well be the pathognomic sign of an intrauterine mechanical ocular trauma caused by midtrimester amniocentesis.

Midtrimester amniocentesis is a procedure that bears a low rate of fetal and maternal complications.[4] Despite the recognized safety of the procedure, fetal injuries caused by amniocentesis occur in an estimated 3 to 4% of the cases.[5–7] Most are innocuous injuries to the skin, which leave only small skin scars. However, serious injuries to the limbs, resulting in loss of a limb, have also been described.[8,9]

Ocular injuries by amniocentesis are undoubtedly rare. In our institution more than 800 amniocenteses were performed and the case described was the only ocular complication. The high risk rate for chromosomal abnormalities in older mothers, ranging from about 2% in the 35 to 39-year-old age group, to over 6% in mothers over 40 years,[10] makes amniocentesis an indispensable tool of modern medicine.

In the present patient, the transabdominal amniocentesis was performed by an experienced gynecologist immediately after an ultrasound scan. Despite this, the eye was injured.

Gynecologists should be advised to direct their needles away from the fetus, especially its head and limbs, which are the two most vulnerable structures. However, it is impossible to avoid all injuries to the fetus, because sudden and strong movements of the fetus may aim the needle directly to the fetus instead of to a pool of amniotic fluid. If amniocentesis is performed under real-time ultrasonographic scanning to detect sudden fetal movement, the rate of complications may be further decreased or eliminated.

Summary

A 6-month-old baby girl with congenital unilateral blindness had an eyelid coloboma and clear evidence of an old vascularized corneal perforation, indicating that the cause of the blindness was an ocular trauma sustained during a midtrimester amniocentesis.

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NOTES, CASES AND INSTRUMENTS

AN IMPROVED SCLERAL SPATULA NEEDLE

LEONARD APT, M.D.
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The spatula needle introduced by Davis and Geck (American Cyanamid Co.) in 1962 has been used extensively in eye surgery. It was devised to permit safer scleral surgery encountered in strabismus and retinal detachment operations. The flat top and bottom surface of the needle (thus the name spatula) separates the scleral layers and thus reduces the chance of inadvertent perforation, which is an important factor, because the sclera is less than 1 mm thick except at the posterior pole.

Although the DO-1 spatula needle has been used with satisfaction for many years, modifications in the design of the point were recommended to the manufacturer, which have improved its performance.

The original design of the DO-1 needle point has remained unchanged over the years (Figure). The tip of the point is diamond-shaped. The shape of the point becomes hexagonal posterior to the tip. The point ends with a shoulder slightly wider than the body of the needle. The widened shoulder was intended to do the following: (1) support the penetrating forces of the needle, (2) stabilize the needle as it passes through the sclera, and (3) enable the proximal portion of the needle and the attached suture to pass more easily through the broadened tract. Only the sides of the needle have cutting edges; consequently the chances of the needle cutting out or down through the scleral wall are lessened.

Two changes were made in the DO-1 needle point design (Figure): (1) the

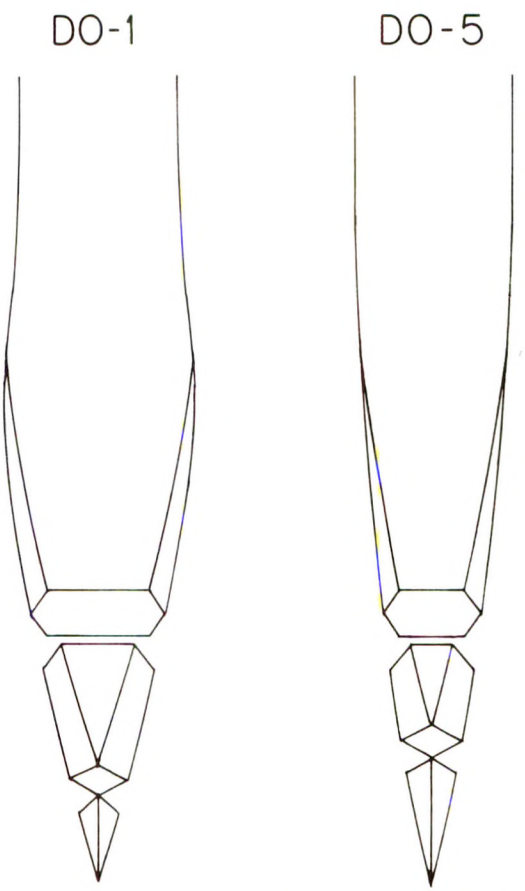

Figure (Apt). DO-1 spatula needle with flat top and bottom surfaces, side cutting edges, diamond-shaped tip, hexagonal point posterior to the tip, and the shoulder of the point slightly wider than the body of the needle. The DO-5 needle is the same as DO-1 except that the tip is lengthened (33%), and the shoulder narrowed (22%).

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diamond-shaped tip was lengthened 33%, from 0.15 to 0.20 mm, to decrease the force needed to penetrate tough scleral tissue; (2) the widened shoulder of the point was reduced 22%, from 0.65 to 0.51 mm, to narrow the tunnel formed by passage of the needle through the sclera.

The slimmed spatula needle (DO-5) penetrates and passes through scleral tissue more easily than the DO-1. It also provides a closer contact between suture and scleral tissue, thereby minimizing the possibility of the suture slipping in its tract or of fluid leaking around the suture.

Except for the revised point design, the slim spatula needle (DO-5) has the same specifications as the DO-1 needle: one-fourth circle curve; 90-degree included angle; radius, 5.16 mm; wire size, 0.356 mm; arc length, 7.94 mm; and chord length, 7.30 mm.

Summary

I devised a new spatula needle (DO-5) that improves the performance of the established DO-1 needle of the Davis and Geck Co. The diamond-shaped tip of the needle was lengthened to improve its penetration force through the sclera and the widened shoulder of the point was narrowed to enable the needle to pass through the sclera more easily and to provide closer contact between suture and scleral tissue.

Acknowledgment

Thomas Ritter, Ph.D., assisted in the design and production of the DO-5 needle.

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THE JOURNAL—1980

The invention of the ophthalmoscope and the special skills required for its use opened up a new world of medicine that directed particular attention toward the eye so that ophthalmology was one of the earliest modern specialties to develop. Even before the introduction of the ophthalmoscope, however, physicians published medical journals limited to the eye and its disorders: Carl Himly and Johann A. Schmidt published three volumes of Ophthalmologische Bibliothek from 1802 to 1807, and Himly published two volumes from 1816 to 1819. Then from 1820 to 1840 thirty volumes of The Journal der Chirurgie und Augenheilkunde were edited by Carl Ferdinand von Graefe and Ph. F. von Walther. Nine more volumes were edited by von Walther and Frederick A. von Ammon between 1843 and 1850. von Ammon edited the Monätschrift für Medicin, Augenheilkunde, und Chirurgie between 1836 and 1840. In 1838 Florent Cunier and M. Schoenfeld began the Annales d'Oculistique et Gynecologie, which became the Annales d' Oculistique under the sole editorship of Cunier in 1839.

The first series of THE AMERICAN JOURNAL OF OPHTHALMOLOGY, begun in 1862, was short-lived. In 1869 the quarterly Archives of Ophthalmology and Otology, edited by Herman Knapp in New York and S. Moos of Heidelberg, appeared. In 1879 it bifurcated into its two basic disciplines. Adolph Alt founded the second series of THE AMERICAN JOURNAL OF OPHTHALMOLOGY in 1884, and this consolidated with five other publications in 1918 when the current series was initiated by Edward Jackson. Today THE AMERICAN JOURNAL OF OPHTHALMOLOGY is the sole American medical journal started by physicians that continues to be managed by physicians and not by a medical society or commercial publisher. The Survey of Ophthalmology is now managed by physicians

but the impetus for its publication came from a publisher.

By 1979 THE JOURNAL had the largest circulation of any ophthalmic journal, paid or unpaid, in the world. It published more editorial pages, more advertising pages, and more original articles than any other ophthalmic journal. The 1,356 pages of paid advertising in 1979 exceeded any previous year.

The domestic subscription income increased by 11% over 1978. The foreign subscription dollar volume increased by 9%. Advertising income was ahead 29%. Reprint income rose 17%. All in all, this is a bright picture of progress. However, in dark contrast, the effects of inflation were evident in all aspects of operation. It cost 35% more to compose, print, and mail THE JOURNAL. Editorial composition increased 38%. Printing costs increased 43%. Mailing costs increased 28%. The cost of providing reprints increased 60%. Office expenses rose by 73%.

An analysis of the per copy production cost of the November 1979 issue of THE JOURNAL proved interesting. The issue carried 154 pages of editorial matter and 126 pages of advertising. Tabular compositon, editorial and advertising composition, camera work, and alterations cost $11,989. The cost per subscription was $0.63. Per copy costs attributed to editorial color inserts were $0.10. Press work cost $0.57 a copy; paper $0.67 a copy; binding $0.09 a copy; wrapping and attaching mailing labels cost $0.07 a

Figure (Newell). Welcome to THE JOURNAL offices.

copy; postage and freight cost $0.48 a copy. (Domestic mailing cost about $0.25 per copy; the foreign mailing was $0.84 per copy.) Computer printout of labels and address changes cost $0.03 each. Production costs thus totalled $2.64 per copy. Review of manuscripts, trafficking with authors, solicitation and processing of subscriptions and advertisments, maintaining the subscription list, auditing, and various business expenses added $1.58 to the cost of each copy. Thus, it cost $4.22 to produce and deliver each copy of the November issue.

To sell a product that costs $4.22 to produce for $1.33 is obviously not sound business. However, advertisers anxious to reach the readers of THE JOURNAL cover the excess cost. Additionally the physician proprietors of THE JOURNAL (Drs. Maumenee, Newell, Norton, Shoch, Straatsma, and Spivey) do not wish to operate THE JOURNAL as a money-making venture any more than they operate their medical school departments for profit. Similar to universities, however, THE JOURNAL must be operated as near to a break-even point as possible or continued operation is impossible.

Publishing in a field in which the major costs of paper and postage far exceed inflation requires careful planning in this new decade. Subscribers who pay for 24 months of THE JOURNAL this month expect the same size, quality, and care in the issue delivered in February 1982. If we continue to experience the same rate of inflation in the next two years as we have in the past year, paper costs will increase 26% and postage 64%. To increase revenue we have raised advertising charges from $310 per black and white page to $350 for 1980. (The Archives of Ophthalmology increased from $285 to $315). We have raised the price of a foreign subscription to $25.

We are investigating a number of systems for reducing costs. Word processing systems look intriguing although generally they seem more compatible with composition than with editing the finished typescript as provided by authors. Conversely, newspapers have found them efficient. Newspapers though are both publisher and printer, combining all the function of writing, editing, composition, printing, and distribution.

The foreign circulation of THE JOURNAL is not large enough to justify printing of an edition abroad. Inasmuch as we do not relate advertising charges directly to increased circulation there may be a basis for maintaining circulation at the current levels and not increasing (the number of subscribers has doubled since 1965). Previously the Board discussed editorial page charges and considered them undesirable. The expenses incurred with peer review (reviewers serve without monetary compensation), careful editing, and quality production are necessary if THE JOURNAL is to maintain its tradition of excellence. Nonetheless those responsible for the proprietorship of THE JOURNAL must be unusually vigilant in the decade to come.

FRANK W. NEWELL

OBITUARY

P. J. Waardenburg, M.D. 1886-1979

Petrus Johannes Waardenburg died at the age of 93 on Sept. 23, 1979. He was one of the first Dutchmen who was interested in anthropogenetics and, being an ophthalmologist and geneticist, he studied the genetics of eye disease in detail. He was one of the founders of clinical genetics in The Netherlands. In this respect he was far ahead of his time. his name is well known throughout the world of ophthalmology and genetics

because of his many publications and because of the syndrome named after him.

The Waardenburg syndrome is an autosomal dominant syndrome consisting of (1) dystopia canthorum; (2) pigmentary abnormalities of the eyes, hair, or skin; and (3) deafness. It was described for the first time in 1951 (Am. J. Hum. Genet. 3:195, 1951). After seeing a patient with deafness and dystopic canthi in 1947 Dr. Waardenburg examined all the pupils in the schools for deaf children in The Netherlands. Of the 1,050 pupils he found 12 affected by this syndrome. In the families of these 12 children he detected altogether 114 patients with similar abnormalities.

Waardenburg was born June 3, 1886, in Nijeveen in the Dutch province of Drenthe, the son of a clergyman. He finished his medical studies in Utrecht in 1911. More or less by chance he became an ophthalmologist because of a vacancy in the Department of Ophthalmology. Two years later he had qualified as an ophthalmologist and he had also finished his thesis under Professor Snellen, Jr., on "Examination in the Human Being on the Heredity of Physiological and Pathological Characteristics of the Eye." At that time the laws of Mendel had only recently been rediscovered (1900) so that his thesis was new at that time.

He published 267 papers and six books. In 1932, he presented "Das menschliche Auge und seine Erbanlagen" ("The Human Eye and Its Geneitc Composition [Design]"). This was the first book on genetic aspects of ophthalmology. Almost every ophthalmologist knows the monumental two-volume work, "Genetics and Ophthalmology," that he published in 1961 and 1963 in collaboration with Professors Franceschetti and Klein, both from Geneva, Switzerland. His last book, written at 84 years of age is entitled "Remarkable Facts in Human Albinism and Leukism," and it was published in 1970 by Royal Van Gorcum of Assen, The Netherlands.

It is remarkable and almost unbelievable that he performed most of his work while as an ophthalmologist in private practice in Arnhem where he worked from 1913 to 1952. I was told that when he came home after a full day of work in his ophthalmic practice he used to say, "It is time I get some work done." Then he worked the whole evening. On the weekends he often visited ophthalmologists in the eastern part of The Netherlands by train to study interesting cases and family pedigrees.

He was lecturer in medical anthropogenetics at the University of Utrecht from 1934 to 1940. From 1952 to 1956 he had a part-time appointment at the University of Leyden and he was head of the Department of Anthropogenetics of the Institute of Preventive Medicine. In 1920 he founded a Genetics Society and a Dutch National Bureau for Anthropogenetics. Out of this the Netherlandish Anthropogenetics Society was founded in 1949. He was its president from 1949 to 1963.

His great scientific achievements have been honored on several occasions. He was honorary member of the Dutch and the Danish Ophthalmological Society and of the Dutch, Italian, and German Anthropogenetic Societies. In 1954 he became doctor honoris causa at the University of Leyden and in 1964 at the University of Münster. In 1957 he became a Knight in the Order of the Dutch Lion. In 1965 he received the Snellen medal, which is given every five years to a Dutch ophthalmologist who has made outstanding contributions. In 1965 the Netherlandish Ophthalmological Society instituted the Waardenburg Prize for theses of promising young ophthalmologists.

Dr. Waardenburg was a wise, gracious

humble man who did much for the name of Dutch ophthalmology. He stimulated many young Dutch ophthalmologists to persevere in the study of genetics in ophthalmology. His work with Professor Henkes of Rotterdam resulted in a joint paper with Pameyer and Henkes on the inheritance pattern of choroideremia (Br. J. Ophthalmol. 44:724, 1960) and in excellent theses by young opthahlmologists such as those of Alkemade (Dysgenesis Mesodermalis), Kurstgens (Choroideremia and Gyrate Atrophy) and Junge (Dystrophia Myotonica). I was priviledged to have the indispensable advice of Dr. Waardenburg when I wrote my thesis on hereditary macular dystrophies and I have fond memories of my frequent visits to his home. In his study he was in his element, surrounded by hundreds of books and thousands of reprints.

Some of his main interests were the study of the macula in red-free light and the studies of diaphanous irides in ocular or generalized albinism.

The pioneering work of Waardenburg in the field of genetics and ophthalmology will be continued in The Netherlands and abroad and his name will certainly live forever.

AUGUST F. DEUTMAN

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Enucleation of Uveal Melanomas

Editor:

The recent excellent article, "An evaluation of enucleation in the management of uveal melanomas" (Am. J. Ophthalmol. 87:741, 1979), by L. E. Zimmerman and I. W. McLean merits correction of certain points made concerning cutaneous malignant melanomas. The authors state: " . . . principal assumptions are that malignant melanomas of the uvea, like those of the skin, have potential to produce metastatic disease early in their course." Further, they state: " . . . uveal melanomas, unlike those of the skin, have no potential for early production of metastatic disease."

Except for nodular melanoma, which comprises but 15% of all cutaneous melanomas,[1,2] primary cutaneous melanomas of the lentigo maligna and superficial spreading type develop through a characteristic biphasic growth pattern.[3] The radial growth phase, which is rarely associated with metastases, lasts from five to ten years before the vertical growth phase, associated with metastases in 35 to 75% of cases, appears. One thus has between five to ten years to recognize and treat these melanomas during a phase when most cases are curable.

It may well be that uveal melanomas, like their cutaneous counterparts, may also be found to have similar "growth patterns," thus explaining the differing observations made on the clinical history of these tumors and their metastasizing potential. This point, I believe, deserves further study as does the possibility of developing intraocular or extraocular methods for safe biopsy of suspicious lesions.

RENE S. RODRIGUEZ-SAINS, M.D.
New York, New York

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human malignant melanomas. Semin. Oncol. 2:83, 1975.

Reply

Editor:

Dr. Rodriguez-Sains brings up an interesting point, one that was discussed even further by Professor Alfred W. Kopf in the Parker Heath Memorial Lecture at the recent meeting of the American Academy of Ophthalmology. Dr. Rodriguez-Sains points out that the premalignant (preinvasive) stage of many cutaneous melanomas lasts five to ten or more years but, in addition, according to the recent studies described by Dr. Kopf, long periods also elapse between invasion of the superficial dermis, invasion of the deep dermis, and invasion of the subcutis; thus, just as changes in our conception of uveal melanomas have taken place during recent years, so also are we beginning to appreciate that cutaneous malanomas are not as rapidly growing or as highly malignant as once thought. By comparison, however, there are still reasons for continuing to have greater concern about cutaneous than about uveal melanomas: (1) mitotic activity is typically much greater in cutaneous than in uveal melanomas, (2) low-grade spindle cell melanomas are common in the uvea but rare in the skin, and (3) metastatic disease is observed much more frequently at the time of initial manifestation among patients with cutaneous melanomas. Dr. Rodriguez-Sains has focused attention mainly on the long period of time that elapses between several premalignant conditions and the truly malignant, invasive stages of cutaneous melanomas, and suggests that perhaps there may be similar "growth patterns" that precede the development of uveal melanomas. Uveal melanomas are more likely to arise in congenital ocular melanocytosis, in the nevus of Ota, in neurofibromatosis, and in large nevi of the uveal tract than in completely normal eyes; but to date, we are not aware of any significant variations in clinical behavior or metastasizing potential that can be correlated with these histogenetically different types of uveal melanomas.

LORENZ E. ZIMMERMAN, M.D.
IAN W. MCLEAN, M.D.
Washington, D.C.

Applanation Tonometry Without Fluorescein

Editor:

I am writing to reply to the question raised by Raymond Smith regarding applanation tonometry without fluorescein in the Correspondence section (Am. J. Ophthalmol. 87:583, 1979).

I wish to emphasize that applanation tonometry without fluorescein will result in marked underestimation of the intraocular pressure. This occurs because one is observing the edge of the meniscus of the tear film rather than the true edge of the applanation prism. As is pointed out in standard textbooks of ophthalmology, for the applanation principle to be correct one must apply force to an area of 3.06 mm^2 in size.

On a series of 100 consecutive eyes I performed applanation tonometry without fluorescein and then with fluorescein and the blue exciting filter. In every case the true intraocular pressure was underestimated by a significant amount. The pressure was lower by a range of 3 to 10 mm Hg and this probably represents the amount of tearing the patient experienced after use of the topical anesthetic.

The use of fluorescein is important so that serious errors in judgement will not be made in the management of patients with glaucoma.

MICHAEL B. RUMELT, M.D.
Creve Coeur, Missouri

Disk Cupping in Childhood Glaucoma

Editor:

I read with great interest the article by A. L. Robin, H. A. Quigley, I. P. Pollack, A. E. Maumenee, and I. H. Maumenee, "An analysis of visual acuity, visual fields, and disk cupping in childhood glaucoma" (Am. J. Ophthalmol. 88:847, 1979). Especially useful was information such as the following: the large eye or hazy cornea was the initial symptom in over half the patients, and the visual field loss was not found in any small (less than 0.4) cups. Further, in "as many as 20% of the patients in the study group . . . an eye was legally blind from (deprivation) amblyopia despite successful IOP lowering that prevented visual field loss."

Because requests for genetic counseling arise in my practice, I was confused by the data presented in the paper, and wonder if the authors could clarify the familial incidence of this problem in their patients.

The authors also studied apparent enlargement of the scleral canal, using the disk:arteriole ratio as it appeared in fundus photographs. As they stated, this ratio was studied to overcome magnification problems in interpreting fundus photographs. Commendably the authors went to this extent to assure their readers of the accuracy of their observations.

On the other hand, the authors did not seem to consider another factor that might cause variation in this ratio, namely, a diminution in the overall caliber of the retinal vasculature secondary to the glaucomatous optic atrophy. They did demonstrate in Table 3 that in glaucomatous adults there is no significant difference in this ratio from normal adults. Conversely, it is possible that glaucomatous adults do not undergo a diminution in the size of the retinal vasculature with glaucomatous optic atrophy, which may occur in childhood glaucoma. Since the authors used their hypothesis of scleral enlargement in a number of ways in discussing their observations, and this hypothesis is, in turn, based only on the disk:arteriole ratio, I wonder if they can provide any histopathologic support for this hypothesis.

PAUL E. ROMANO, M.D.
Chicago, Illinois

Reply

Editor:

Our article's intention was to assess the long-term visual acuity, field loss, and disk cupping in childhood glaucoma and not its heredity as was done previously by Merin and Morin.[1] Data on family history were included to demonstrate the similarity of our patients to those in other series that reported a contributory family history varying from 4 to 25%.[1-3] The results of these studies, including ours, suggest that families with one affected member should be counseled that they have an increased chance of producing an affected offspring.

Dr. Romano raises the possibility that retinal vessel caliber narrowing might explain the high disk:arteriole ratio observed in our patients. We believe this is unlikely, as major retinal vascular changes are not thought to occur either clinically or histologically in adults with glaucoma.[4] We do, however, have histopathologic confirmation of scleral canal enlargement in the eyes of children with glaucoma. This material was not included in our article because the eyes in which we obtain histological information are subject to the objection that they are end-stage eyes with no visual function. These eyes therefore represent the far end of this disease spectrum. Nonetheless, we have detailed measurements of a number of enucleated eyes, one of which illustrates the findings. The right eye of a 22-year-old black man was recently enu-

TABLE

DISK:ARTERIOLE RATIO

Group	No. of Eyes	Horizontal Disk:Arteriole Ratio*	Horizontal Standard Error	Vertical Disk:Arteriole Ratio*	Vertical Standard Error
Childhood glaucoma	49	18.3 ± 3.5	0.50	17.3 ± 3.4	0.49
Normal adults	40	14.6 ± 2.4	0.38	15.7 ± 2.9	0.46
Glaucomatous adults	46	14.2 ± 1.9	0.28	15.2 ± 2.0	0.29
Normal children	17	15.2 ± 1.8	0.44	15.8 ± 1.9	0.47

*Mean ± one standard deviation.

cleated because of no light perception and pain caused by increased intraocular pressure. Ophthalmoscopy disclosed no apparent neuroretinal rim. The globe's diameter was 27 × 27.5 × 32.5 mm. The horizontal corneal diameter was 15 mm. Before embedding but after fixation, no neuroretinal rim was evident. The scleral canal (and cup) measured 3.7 mm in all dimensions. In paraffin sections, the maximum diameter of the disk from the termination of Bruch's membrane to the same landmark on the other side was 4.0 mm. These measurements of the scleral canal are more than twice normal, confirming the existence of scleral canal enlargement as suggested by our disk:arteriole ratio estimates in patients with lesser degrees of damage.

Additionally, we have since measured the disk:arteriole ratios in 17 eyes of nine normal children (Table). Using the normal deviate test, we found no significant difference between the disk:arteriole ratio in either dimension when comparing eyes of normal children and normal adults. However, the disk:arteriole ratios were significantly larger in children with glaucoma than in normal children in both the horizontal ($P < .001$ and vertical ($P < .05$) dimensions. The disk:arteriole ratio is apparently not age-related but probably dependent, as suggested by histology, upon scleral canal (disk) diameter.

The disk:arteriole ratio aids in the assessment of disk cupping in visually functioning eyes since direct measurement of their scleral canal size is not possible. In these eyes we must make every effort to determine whether cupping is caused by axonal loss or scleral canal enlargement. Our disk:arteriole ratio confirms the clinical impression that disk cupping in children with glaucoma can be due to scleral canal enlargement alone.

ALAN L. ROBIN, M.D.
HARRY A. QUIGLEY, M.D.
IRVIN P. POLLACK, M.D.
A. EDWARD MAUMENEE, M.D.
IRENE H. MAUMENEE, M.D.
Baltimore, Maryland

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BOOK REVIEWS

Tuberous Sclerosis. Edited by Manuel R. Gomez. New York, Raven Press, 1979. Hardcover, 264 pages, foreword, preface, table of contents, bibliography, index, 92 black and white figures, 3 color plates. $22.50

This readable text promises to be the definitive reference work on the subject of tuberous sclerosis for many years to come. It contains a bibliography of 352 references, spanning the years from the first incomplete description by von Recklinghausen in 1862 and its later more complete exposition by Bourneville in 1880 to the present.

Tuberous sclerosis, a syndrome rarely seen by the average physician, is nevertheless an important condition, genetically determined and characterized by hamartomas of the skin, brain, retina, kidney, heart, lung and other organs, and often by intractable seizures and mental deterioration.

This text brings together into one source-work the many accounts of the widespread anatomic distribution and diverse manifestations of tuberous sclerosis.

The stimulating foreword by Macdonald Critchley and an introduction by the editor, Manuel R. Gomez, are followed by 13 chapters on the various aspects of the disease. Dr. Gomez wrote six of the chapters, beginning with the first chapter on the historical aspects. In his second chapter, "Clinical Experience at Mayo Clinic," he describes the findings in a remarkable series of 160 patients. His later chapters are as follows: "Neurologic and Psychiatric Symptoms." "On Other Visceral," "Vascular and Osseous Lesions," "Related Disorders," and a final chapter written with Nancy L. Kuntz, "Genetics, Population Studies and Pathogenesis."

Other chapters, written in fairly uniform expert fashion by authorities on various aspects of tuberous sclerosis, are concerned with X-ray diagnosis, electroencephalography, neuropathology, dermatology, cardiology, and renal involvement.

The chapter on the ocular manifestations of the disease, written by Dennis Robertson, is a particularly outstanding contribution.

In my opinion, the substitution of the acronym, TS, for the proper term, tuberous sclerosis, throughout the book, is not a happy expedient. The saving of space is a negligible factor that in no way compensates for the disturbance it creates for the reader. Nevertheless, this is in general an excellent work, highly recommended to all clinicians.

ROBERT W. HOLLENHORST

Diseases of the Cornea. By Merrill Grayson. St. Louis, C. V. Mosby, 1979. Hardcover, 552 pages, preface, table of contents, index, appendix, 280 black and white figures, 151 color figures. $72.50

This latest book, of Dr. Grayson will be a welcome addition to any ophthalmologist's library. Although the text is oriented primarily toward the instruction of residents in ophthalmology, students at all levels, including practicing ophthalmologists, will find it highly useful, well written, and complete. Insofar as the quality of the text and illustrations is concerned, this book can be rated at least one log unit higher than Grayson's previous effort in this field.

The text is organized in a logical fashion, beginning with anatomic considerations and ending with a short but most useful appendix on the laboratory investigation of patients with external diseases of the eye. Each chapter begins with a tabular listing of the topics that are to be discussed, and these individual subjects are set apart, one from another, by boldfaced titles that allow the reader easy access to the material he wishes to find. The index at the end of the book is detailed, and this, too, is useful to the reader who wishes to look up specific information.

One chapter to which I paid particular-

ly close attention was entitled "Immune and Mucous Membrane Diseases." Because of the number of extraordinarily rapid developments in this field, this chapter was in many ways the most difficult to write. Grayson presents a good summary of general immunology in this chapter, although the material is, of necessity, briefly and somewhat superficially treated. Because of failure to explain certain subjects fully, questions are occasionally left in the mind of the reader. For example, on page 286 the author states "IgM has been detected in the conjunctiva, cornea, and beneath the epidermis, but is primarily intravascular." On page 287, he states "No IgM occurs in the human cornea." This creates a conflict, which could have been resolved by stating that "because of its molecular size, IgM cannot diffuse, to any significant degree, from the limbal circulation into the corneal stroma."

The copious illustrations are generally of good quality. The presence of 151 color figures has undoubtedly driven the price up to a soaring $72.50. One wonders whether so many color photographs can be justified. Sometimes a black and white photograph of good detail can show more than a color photograph, particularly when arrows are used. For example, Figure 14-7 is a color photograph of Trantas dots. Color is wasted here. For lack of contrast, one cannot discern the dots, and the necessary arrows are missing. Similarly, one cannot discern the band keratopathy in Figure 26-7. In Chapter 18 ("Mucopolysaccharidoses") the deformity of a child's hand (Fig. 18-2) and the general shape of her face (Fig. 18-4) might have been shown just as well in black and white.

I am happy to own a copy of Grayson's Diseases of the Cornea and will be happier still to own a second edition. The current book has its share of correctable mistakes (misprints, inverted pictures, and the like) but because of its general value, it will certainly survive to a second edition.

G. RICHARD O'CONNOR

Visual-Evoked Potentials in Central Disorders of the Visual System. By Kenneth A. Kooi and Robert E. Marshall. Philadelphia, Harper and Row Publishers, Inc., 1979. Hardcover, 169 pages, preface, appendix, index, 94 black and white figures. $25

The authors bring a wealth of experience to their consideration of the visual-evoked response. Their exposition of methods and techniques is accurate and thorough. Their presentation is particularly strong when they use isopotential maps of surface potentials recorded from as many as 24 sites on the scalp.

Although pathologic findings may be pointed out, pathognomonic findings still escape us. Lateral asymmetries and abnormal wave forms abound in patients with field defects and aphasias as presented in the book. However, abnormalities characteristic of a particular disease cannot be defined.

The nature of the problem is easy enough to understand. The visual-evoked response (VER) is a timed set of potential changes that take a devious course through a nonhomogenious conductor, the brain, and are recorded on the curved surface of the conducting solid after passing through skull and scalp, which have their own electrical properties. No one should be amazed that the record and the intracranial event do not have one-to-one correlation. It is no discredit to the authors that the core problem of the VER, which has eluded all other workers in the field, has eluded them also.

There are a few established valid applications of the VER. These depend

on binocular differences where a known healthy eye exists as control. Otherwise, despite the elegance of the hardware, the considerable thought expended, and the care spent in data reduction, recording of the FER is still a method searching for an application.

ALBERT M. POTTS

Physiology of the Human Eye and Visual System. Edited Raymond E. Records. Hagerstown, Harper and Row, Publishers, Inc., 1979. Hardcover, 691 pages, preface, bibliography, index, 106 black and white figures, 10 color figures. $45

This new textbook is a pleasure to review. The editor, Raymond E. Records, has gathered a group of individuals to write on specific areas of the physiology of the eye and visual processes. In the preface, he states that this volume functions both as a reference work and as a textbook. He has succeeded admirably, for virtually without exception each segment of the book can be viewed as a complete and up-to-date review of the physiology of that system under discussion. In this context the clinical applications of our physiologic knowledge are well covered. With few exceptions bibliographies in each section are also complete and provide even further help to the reader.

It takes a courage on the part of both the author and the publisher to put out a textbook of the physiology of the eye when faced with the knowledge that Adler's "Physiology of the Eye" is a recognized classic in this field and is on the shelves of virtually every ophthalmologist, as well as being a widely used text in the libraries of the visual researcher. Thus, is there any way that this text improves upon Adler's textbook and if not, has it any real place for those in the field of vision? In my view, this book does not offer any real improvement over Adler's textbook; indeed, all areas are similarily covered. However, this text deserves to be read because of the consistent excellence of the various chapters. It is always worthwhile to read the opinions of experts in their areas to learn their differences in perspective and their emphasis on particular areas, often within their own field of expertise.

This text is most worthwhile and can be beneficial to all in the ophthalmic community.

RONALD E. CARR

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Acta Ophthalmologica

AGE VARIATIONS IN NORMAL HUMAN CONTRAST SENSITIVITY. Derefeldt, G., Lennerstrand, G., and Lundh, B. (Dept. Ophthalmol., Linköping Univ., Sweden). Acta Ophthalmol. 57:679, 1979.

In recent years contrast sensitivity of the human eye has been found to be abnormal in some neurologic states. There is apparently also a decrease in contrast sensitivity in glaucoma. It is therefore important to establish base lines against which to measure these decreases. The authors point out that one of the factors that affects the response is age. There appears to be no difference in contrast sensitivity between the ages of 6 and 40 years but for ages above 60 there is a loss of sensitivity in the middle and high frequency regions. This must be taken into account when interpreting the results of studies in pathologic states. (3 figures, 2 tables, 25 references)—David Shoch

Annals of Neurology

ALEXIA, WITHOUT AGRAPHIA, DUE TO BRAIN TUMOR: A REVERSIBLE SYNDROME. Turgman, J., Goldhammer, Y., and Braham, J. (Dept. Neurol., Chaim Sheba Med. Ctr., Tel Hashomer, Israel). Ann. Neurol. 6:265, 1979.

Alexia without agraphia or word blindness is characterized by loss of reading without the loss of capacity to write. It usually results from a lesion in the dominant calcarine area and the splenium of the corpus callosum disconnecting the functioning calcarine area of the healthy occipital lobe from its connections with the speech center in the angular gyrus of the dominant hemisphere. Such patients can write spontaneously or on command but are unable to read back their own handwriting. The most frequent cause for this is ischemic cerebral vascular disease and therefore the entity is usually irreversible. In the patient reported here a craniotomy was done to remove a posterior fossa lesion following which the patient developed alexia without agraphia. A further mass was then found in the left occipital lobe and on removal of this the alexia gradually improved. (2 figures, 1 table, 16 references)—David Shoch

Archives of Ophthalmology

DIPIVEFRIN AND EPINEPHRINE TREATMENT OF ELEVATED INTRAOCULAR PRESSURE: A COMPARATIVE STUDY. Kass, M. A., Mandell, A. I., Goldberg, I., Paine, J. M., and Becker, B. (Glaucoma Ctr., Dept. Ophthalmol., Washington Univ. School of Med., St. Louis, Mo.). Arch. Ophthalmol. 97:1865, 1979.

Every 12 hours 0.1% dipivefrin was administered to one eye and 2% epinephrine hydrochloride was administered to the fellow eye of 42 patients with primary open-angle glaucoma or ocular hypertension in a randomized, double-masked study lasting three months. Dipivefrin produced similar percent reductions in intraocular pressure (18.6%) to epinephrine (21.0%), as well as similar increases in outflow facility and pupil diameter. A significantly lower incidence of burning and stinging after drug instillation was noted with dipivefrin therapy. This study supported the contention that dipivefrin is an effective and safe alternative to epinephrine therapy for the reduction of elevated intraocular pressure. (3 tables, 9 references)—Authors' abstract

ASPIRATION CYTODIAGNOSIS OF EYELID TUMORS. Jakobiec, F. A., and Chattock, A. (Algernon B. Reese Lab. of Ophthal. Pathol., Edward S. Harkness Eye Inst., New York, N.Y.). Arch. Ophthalmol. 97:1907, 1979.

In five patients, specimens of discrete, subepidermal eyelid tumors were successfully aspirated with 22- to 24-gauge spinal needles and diagnosed cytologically. The simplicity, rapidity of diagnosis, and high accuracy of cytodiagnosis should make it a popular method for the evaluation of clinically puzzling subepidermal eyelid tumors. (13 figures, 11 references)—Authors' abstract

DISAPPEARANCE OF KAYSER-FLEISCHER RINGS AFTER LIVER TRANSPLANTATION. Schoenberger, M., and Ellis, P. P. (Dept. Ophthalmol., Univ. Colorado Med. Ctr., Denver, Colo.). Arch. Ophthalmol. 97:1914, 1979.

Kayser-Fleischer rings were observed in a 14-year-old boy with progressive liver disease. Laboratory data supported a diagnosis of hepatolenticular degeneration (Wilson's disease). Therapy with chelating agents was initiated, but discontinued because of side reactions. Successful liver homotransplantation was performed. The Kayser-Fleischer rings gradually faded and had completely disappeared by six years postoperatively. (4 figures, 1 table, 11 references)—Authors' abstract

DIPIVEFRIN AND ECHOTHIOPHATE: CONTRAINDICATIONS TO COMBINED USE. Abramovsky, I., and Mindel, J. S. (Depts. Ophthalmol., and Pharmacol., Mount Sinai School of Med., New York, N.Y.). Arch. Ophthalmol. 97: 1937, 1979.

A study was undertaken to determine whether the antiesterase activity of echothiophate iodide would prevent the conversion of dipivefrin to epinephrine. Dipivefrin was administered singly and in combination with echothiophate to 24 adult rabbits. Administration of dipivefrin lowered the intraocular pressure 8 ± 1 mm Hg ($P < .001$). When echothiophate was given before and concomitant with dipivefrin, there was no further decrease in intraocular pressure compared with that produced by echothiophate alone (5 ± 1 mm Hg). Addition of epinephrine to eyes receiving dipivefrin plus echothiophate resulted in a significant additional decrease in intraocular pressure of 4 ± 1 mm Hg ($P < .001$). When echothiophate was given after dipivefrin had lowered the intraocular pressure and both drugs were continued, the intraocular pressure rose to baseline levels. These results fit the theory that the esterase converting dipivefrin to epinephrine is inactivated by cholinesterase inhibitors. The clinical use of cholinesterase inhibitors and dipivefrin may be contraindicated. (4 figures, 1 table, 9 references)—Authors' abstract

PROLIFERATIVE ENDOTHELIOPATHY WITH IRIS ABNORMALITIES: THE IRIDOCORNEAL ENDOTHELIAL SYNDROME. Eagle, R. C., Font, R. L., Yanoff, M., and Fine, B. S. (Dept. Ophthal. Pathol., Armed Forces Institute of Pathology, Washington, D.C.). Arch. Ophthalmol. 97:2104, 1979.

Pathologic and clinical evidence suggests that the iris nevus syndrome, Chandler's syndrome, and essential iris atrophy represent a continuum of clinical manifestations of a single disease process involving proliferation of the corneal endothelial and characteristic iris abnormalities; the latter may be secondary to variations in the pattern, rate, and extent of endothelial proliferation. The authors suggest the term "proliferative endotheliopathy" to emphasize the common pathogenetic role of corneal endothelial proliferation in all three entities (iris nevus syndrome, Chandler's syndrome, and essential iris atrophy). A more succinct alternate term is "the iridocorneal endothelial syndrome". (9 figures, 24 references)—Authors' abstract

360 DEGREE PROPHYLACTIC CRYORETINOPEXY: A CLINICAL AND EXPERIMENTAL STUDY. Robertson, D. M., and Priluck, I. A., (Dept. Ophthalmol., Mayo Clinic, Rochester, Minn.). Arch. Ophthalmol. 97:2130, 1979.

Complications occurred after 360 degree prophylactic cryoretinopexy in three of six eyes in which fellow eyes had previously developed aphakic retinal detachment. Two of the six prophylactically treated eyes developed retinal detachment in advance of anticipated cataract surgery, and a third developed vitreitis and progressive preretinal membrane formation after uncomplicated cataract extraction. In an experimental study with rhesus monkeys, preretinal membrane formation was produced by administering heavy freezes with 360 degree cryoretinopexy. Although the quantities of cold were considered excessive for clinical use, the cryoretinopexy used clinically in this series must also be considered excessive. The use of 360 degree cryoretinopexy in the management of eyes at high risk for retinal detachment must be considered judiciously. Particular caution must be exercised in administering cryoretinopexy to nondetached retinas so as to avoid heavy freezes, which destroy the inner retinal layers. (3 figures, 1 table, 21 references)—Authors' abstract

Bulletin of the World Health Organization

THE RISK OF OPTIC ATROPHY FOLLOWING SURAMIN TREATMENT OF OCULAR ONCHOCERCIASIS. Thylefors, B., and Rolland, A. (WHO Onchocerciasis Control Program, Ouagadougou, Upper Volta). Bull. WHO 57:479, 1979.

Suramin is one of the few non-metallic compounds effective in the treatment of protozoal infections. It is used a great deal in the treatment of onchocerciasis but there have been reports of ensuing optic atrophy. In this study, 25 patients with onchocerciasis were treated with weekly injections of suramin while a comparable group of 23 were untreated. Before treatment in 1975 there was one patient in each group who showed an optic atrophy. Three years later the same patient was present in the untreated group but there were now four additional patients in the treated group who demonstrated an optic atrophy. No other ocular lesions had occurred in the intervening three years but there seems to be some indication that there is a risk of optic atrophy with the use of suramin. (1 table, 10 references)—David Shoch

Investigative Ophthalmology and Visual Science

TAPETUM DISORGANIZATION IN TAURINE-DEPLETED CATS. Wen, G. Y., Sturman, J. A., Wisniewski, H. M., Lidsky, A. A., Cornwell, A. C., and Hayes, K. C., (Dept. Pathol. Neurobiol., Inst. for Basic Research in Mental Retardation, Staten Island, N.Y.). Invest. Ophthalmol. Vis. Sci. 18:1200, 1979.

A severe disorganization of the lattice arrangement of tapetal rods occurs in cats nutritionally deprived of taurine. This is the first reported example of a nutritionally related degeneration of tapetal cells. The tapetal cell degeneration, along with the previously noted photoreceptor degeneration in taurine-depleted cats, suggests that taurine plays a vital role in maintaining the structural integrity of some biological structures. The visual evoked potentials were severely reduced in taurine-depleted cats as were the electroretinogram responses, as previously noted, indicating that they are deficient in light processing. These results also emphasize the importance of dietary taurine for the maintenance of normal structure and function of the eye, at least in the cat. (2 figures, 2 tables, 13 references)—Authors' abstract

Japanese Journal of Ophthalmology

THE CLINICAL SIGNIFICANCE OF DIURNAL PRESSURE VARIATION IN PRIMARY OPEN-ANGLE GLAUCOMA. Horie, T., and Kitazawa, Y. (Dept. Ophthalmol., University of Tokyo, School of Medicine, Tokyo, Japan). Jap. J. Ophthalmol. 23:310, 1979.

Intraocular pressure was measured with a Goldmann applanation tonometer in 21 normal individuals, 38 ocular hypertensives without field loss and 39 patients with primary open-angle glaucoma every hour for 24 hours. In 16 subjects hourly tonometry was repeated twice at the interval of one week. Statistically highly significant correlation was noted between the characteristic factors of the diurnal curves comprising peak and trough pressures, magnitude of diurnal pressure variation and mean pressure throughout 24 hours in the test population studied. However, no significant difference in the magnitude of diurnal pressure variation was demonstrated between the ocular hypertensives and the primary open-angle glaucoma patients matched according to age, sex, and the peak pressure level. In primary open-angle glaucoma patients the age was inversely related to the magnitude of diurnal pressure variation. A statistically significant linear relationship was demonstrated between the peak pressure and the intraocular pressure at 11 a.m. and 12 noon. A similar relationship was disclosed between the trough pressure and the intraocular pressure at 12 midnight and 2 a.m. The validity to predict the peak or trough pressure on the basis of a single pressure measurement was substantiated by substituting the data from the external samples into the derived equations. A highly significant correlation coefficient was demonstrated between the measured and the predicted values on the basis of best fitted cosine curves in the majority of

the subjects. The findings support the concept that the diurnal pressure variation has a circadian rhythm in a chronobiological sense. It was demonstrated that the pressure variation between the two eyes in each individual varied synchronously, and the difference in pressure between the two eyes remained remarkably constant for the 24-hour period, not only in the normal but in the ocular hypertensives and the glaucomatous patients as well. The peak and the trough pressures were almost identical and took place at almost the same time of the day on the repeated determinations at the interval of one week. (14 figures, 16 tables, 62 references)—Authors' abstract

Journal of Allergy and Clinical Immunology

TOPICAL OCULAR ADMINISTRATION OF CROMOLYN SODIUM FOR TREATMENT IN SEASONAL RAGWEED CONJUNCTIVITIS. Welsh, P. W., Yunginger, J. W., Tani, D. G., Toussaint, N. F., Larson, L. A., Bourne, W. M., and Gleich, G. J. (Depts. Pediatr., Int. Med., Ophthalmol., and Immunol., Allergic Diseases Research Lab., Mayo Clinic, Rochester, Minn.). J. Allergy Clin. Immunol. 64:209, 1979.

A group of patients with seasonal ragweed conjunctivitis were divided into two groups; half of these received a 4% solution of cromolyn sodium and the control patients received placebo drops. All patients in this study had IgE antibody levels of 100 ng/ml or greater. Those patients receiving the cromolyn sodium had a significant reduction in rhinorrhea and nasal congestion but there was no significant reduction in eye symptoms. No other side effects were noted. (7 figures, 3 tables, 9 references)—David Shoch

Journal of the American Medical Association

PREDICTION OF OUTCOME OF SURGERY AND ANESTHESIA IN PATIENTS OVER 80. Djokovic, J. L., and Hedley-Whyte, J. (Dept. Anaesthesia, Harvard Med. School and Beth Israel Hosp., Harvard Univ., Boston, Mass.). J.A.M.A. 242:2301, 1979.

The authors studied the outcome of surgery in 500 patients over 80 years of age. Hospital mortality within one month of surgery was 6.2%. The American Society of Anesthesiologists Class 1 to 5 preoperative evaluation scale was useful in predicting death—less than 1% of Class 2 patients died, 4% of Class 3, and 25% of Class 4. Six of seven perioperative deaths were caused by mesenteric infarction. Myocardial infarction was the leading cause of postoperative death. One must note that these patients all had either general or regional anesthesia and only four of them had eye surgery. (4 figures, 2 tables, 16 references)—Authors' abstract

CARDIAC ARREST FOLLOWING FLUORESCEIN ANGIOGRAPHY. Cunningham, E. E., and Balu, V. (Dept. Int. Med., State Univ. of New York, Buffalo, N.Y.). J.A.M.A. 242:2431, 1979.

A 61-year-old man with a history of chronic stable angina was hospitalized for evaluation of accelerated angina of two weeks duration. Coronary angiography was followed by acute oliguric renal failure considered secondary to the injection of radiopaque contrast material. He recovered from this with the aid of hemodialysis and some three months later underwent fluorescein angiography to rule out minimal diabetic changes. Twenty minutes after the injection of fluorescein the patient suddenly collapsed and resuscitative efforts were unsuccessful. The patient was pronounced dead 45 minutes after the injection of fluorescein. It is possible that the fluorescein dye had a direct vasospastic effect but it is probably more likely that a vasovagal reaction resulted in bradycardia and a fall in myocardial perfusion and oxygen supply. (4 references)—David Shoch

Lancet

FISH-EYE DISEASE: A NEW FAMILIAL CONDITION WITH MASSIVE CORNEAL OPACITIES AND DYSLIPOPROTEINAEMIA. Carlson, L. A., and Philipson, B. (Depts. Int. Med., and Ophthalmol., Karolinska Hosp., Stockholm, Sweden). Lancet 2:921, 1979.

A man and his three daughters had massive corneal opacities called in their home village

"fish-eye disease" because of the resemblance of the eyes to those of boiled fish. The two living daughters had the same dyslipoproteinaemia, characterised by normal serum cholesterol but raised serum triglycerides, raised very-low-density lipoproteins, strikingly high levels of low-density lipoprotein triglycerides. Low-density lipoprotein contained normal sized as well as abnormally large particles and a 90% reduction in the level of high-density lipoprotein cholesterol. Lecithin: cholesterol acyltransferase activity and the percentage of plasma cholesterol esters were normal, which excluded lecithin: cholesterol acyltransferase deficiency. Normal electrophoretic mobility of high-density lipoprotein as well as other lipoprotein findings excluded Tangier disease. The clinical and laboratory abnormalities in fish-eye disease are atherosclerosis at old age, visual impairment, and dense corneal opacification. Fish-eye disease thus differs both clinically and in its lipoprotein abnormalities from lecithin: cholesterol acyltransferase deficiency and Tangier disease. (3 figures, 3 tables, 13 references)—Authors' abstract

Transactions of the Ophthalmological Societies of the United Kingdom

VARIABLE FOCUS SPECTACLES. Wright, B. M. (Clinical Res. Ctr., Harrow, England). Trans. Ophthalmol. Soc. U. K. 98:84, 1978.

The author has devised a three-layered spectacle lens; the outer and inner layers of which are glass and the center which is filled with a fluid similar to the glass in index of refraction. With a small bellows in the temple he is able to push fluid into the hollow space thus increasing the refractivity by as much as two to three diopters and thus making the spectacle useful at near. Pulling back on the bellows removes the fluid which returns the lenses to plano and thus useful for distance. If a correction is present this can be ground into the anterior glass layer. These variable focus spectacles are apparently in the process of being developed commercially. (2 figures, 2 references)—David Shoch

ROLE OF CARDIOVASCULAR DISEASE IN THE PATHOGENESIS OF RHEGMATOGENOUS RETINAL DETACHMENTS. Zinn, K. M., Field, R., and Schepens, C. L. (Retina Ser., Mass. Eye and Ear Infirm., Dept. Ophthalmol, Harvard Med. School, Boston, Mass.). Trans. Ophthalmol. Soc. U. K. 98:134, 1978.

In 100 patients with fresh rhegmatogenous retinal detachments complete ocular and physical examinations including electrocardiograms were carried out. The incidence of coronary artery disease and systemic hypertension in these patients with retinal detachments was much greater than that found in the general population of similar age and sex. It is suggested that the common entity present in all these vascular diseases is ischemia and that the retinal detachments may result from ischemia of the retina and choroid. This would suggest that retinal detachments are only one element of generalized vasculopathies that involve coronary arteries, pulmonary vasculature, and perhaps the renal circulation in patients with systemic hypertension. (2 figures, 7 tables, 35 references)—David Shoch

VISUAL DISABILITIES OF OCULOCUTANEOUS ALBINISM AND THEIR ALLEVIATION. Taylor, W. O. G. (Ayr, Scotland). Trans. Ophthalmol. Soc. U. K. 98:423, 1978.

Albinotics have a variety of ocular problems related to morphologic changes in the eye. The central vision is usually poor and in histologic studies done in albinos it is found that the retina is six to eight cells thick in the macula area rather than containing only receptors. The photophobia is caused by the marked pigment deficiency in the iris and retina. Associated with these is nystagmus and frequent strabismus. Since the albino has the same complement of pre-melanosomes as normal individuals it appears that the deficiency in melanin production is within the cell. In those albinos who are tyrosinase-negative there is probably no hope for treatment but in a tyrosinase-positive albino the feeding of large amounts of tyrosine has been tried without success. The author recommends tinted lenses to help with the photophobia and finds that the new photochromic lenses are particularly useful. One may also use contact lenses with opaque scleral portions and painted irides. A side effect which has been beneficial is that the weight of the lenses tends to reduce the excursion of the nystagmus. Low vision aids are obviously useful when required. (28 figures, 2 tables, 143 references)—David Shoch

DISSEMINATED INTRAVASCULAR COAGULOPATHY. Martin, V. A. F. (Dept. Ophthalmol., Royal Victoria Hosp., Belfast Ireland). Trans. Ophthalmol. Soc. U. K. 98:506, 1978.

Disseminated intravascular coagulation is not a disease but a pathological process with widespread thrombus formation in small vessels; it occurs in many systemic conditions that stimulate the intravascular clotting mechanism. There may be widespread tissue involvement, and any tissue in the body may be affected, especially in the kidney, brain, liver, heart, and lungs. This abnormal coagulation is now commonly referred to as disseminated intravascular coagulopathy. It is prone to occur in obstetrical complications, in cancer, after transplantations, and where there has been tissue damage, such as burning, crushing, and surgery, all of which release thromboplastin into the circulation. It may also occur in Gram negative bacterial systemic infections, in antigen-antibody reactions, and in thrombotic thrombocytopenic purpura. When the eye is involved, the thrombi occur in the choriocapillaris, and are usually limited to the submacular and peripapillary choroid. The anterior parts of the eye generally escape involvement. Visual symptoms may be early, and may be due to central choroidopathy or to secondary retinal detachment. (8 references)—Author's abstract

Transactions; Pennsylvania Academy of Ophthalmology and Otolaryngology

PSEUDOPHAKIC RETINAL DETACHMENT. Tasman, W. (Dept. Ophthalmol., Thomas Jefferson Univ., Philadelphia, Pa.). Trans. Pa. Acad. Ophthalmol. Otolaryngol. 32:139, 1979.

The authors studied 252 patients with retinal detachments following cataract extraction and intraocular lens implant. On the average, detachment occurred 87 days after the implant which is much shorter than the usual aphakic detachment where the average elapsed time is about 37 months. More importantly the retinal breaks could not be identified in 18% of the cases which is 2 ½ times greater than the failure to identify retinal breaks after conventional intracapsular cataract extraction. Thirty-five percent of the patients attained 20/40 (6/12) or better vision, a lower figure than the visual results in aphakic detachments where a conventional intracapsular procedure had been performed. On the basis of this study the author feels that an intraocular lens is contraindicated when there is a history of a retinal break or retinal detachment in the fellow eye, a family history of retinal detachment or vitreous loss at the time of surgery. (1 figure, 8 references)—David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

Send News Items double-spaced to News Editor, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

INTERNATIONAL SYMPOSIUM ON INTRAOCULAR TUMORS

An International Symposium on Intraocular Tumors will be held May 17-21, 1981, in Schwerin, German Democratic Republic. For further information, write Dr. K. P. Lommatzsch, Augenklinik, Stadtisches Klinikum Berlin-Buch, Karower Strasse 11, 1115 Berlin, German Democratic Republic (East Germany).

IRISH OPHTHALMOLOGICAL SOCIETY: ANNUAL MEETING

The annual meeting of the Irish Ophthalmological Society will be held in Dublin, April 25 and 26, 1980. For further information, write Dr. G. P. Crookes, Hon. Secretary, Irish Ophthalmological Society, 18, Fitzwilliam Place, Dublin 2, Ireland.

AUSTRALIAN NATIONAL COUNCIL OF AND FOR THE BLIND: INTERNATIONAL CONFERENCE

The Australian National Council of and for the Blind will sponsor an International Conference on Low Vision May 19-21, 1980. For further information, write Mr. Lindsay McMillan, Conference Organiser, Association for the Blind, H. M. Lightfoot Centre, 454 Glenferrie Road, Kooyong, Victoria, 3144 Australia.

CANADIAN OPHTHALMOLOGICAL SOCIETY: 43RD ANNUAL MEETING

The Canadian Ophthalmological Society will hold its 43rd Annual Meeting June 8-11, 1980. For further information, write the Canadian Ophthalmological Society, P. O. Box 8844, Ottawa, Ontario, Canada K1G 3G2.

ISRAEL INTERNATIONAL SYMPOSIUM ON GLAUCOMA

The Israel International Symposium on Glaucoma will be held in Tel Aviv, Israel, Sept. 3-5, 1980. For further information, write Secretariat, P.O.B. 16271, Tel Aviv, Israel.

ELISABETH HOSPITAL: INTERNATIONAL LENS IMPLANT COURSE

An international lens implant course will be held at Elisabeth Hospital, Sluiskil, Netherlands, Sept. 10-11, 1980. For further information, write Ms. Mary van der Peijl, Abeelstraat 3, 4537 XR Terneuzen, The Netherlands.

OPHTHALMOLOGICAL SOCIETY OF SOUTH AFRICA: ANNUAL CONGRESS

The Annual Ophthalmological Society of South Africa Congress will be held May 4-8, 1980. For further information, write The Secretary, P. O. Box 2409, Johannesburg 2000, South Africa.

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY: ELEVENTH ANNUAL WILLIAM L. BENEDICT LECTURE

The Minnesota Academy of Ophthalmology and Oto-Laryngology presented its Eleventh Annual William L. Benedict Lecture at its meeting on Jan. 11, 1980. Robert T. Schaller, M.D., was the guest speaker. His topic was "Medical Experiences in the American K - Z climb." Dr. Benedict was president of the Ophthalmic Publishing Company at the time of his death in 1969.

ST. FRANCIS HOSPITAL, ROSLYN, NEW YORK: OPHTHALMOLOGY SEMINAR

St. Francis Hospital, Roslyn, New York, will hold a seminar, "Ophthalmology: What's New In . . . ," March 29, 1980. For further information, write Sean P. Joyce, Manager, Training and Education, St. Francis Hospital, Port Washington Blvd., Roslyn, NY 11576.

UNIVERSITY OF ILLINOIS: ANTERIOR AND POSTERIOR SEGMENT VITRECTOMY COURSE

The University of Illinois College of Medicine Department of Ophthalmology, will hold an anterior and posterior segment vitrectomy course March 28 and 29, 1980. Registration fee is $350. For further information, write University of Illinois at the Medical Center, Office of Continuing Education Services, 1853 W. Polk St., Room 144, Chicago, IL 60612.

ROCHESTER OPHTHALMOLOGICAL SOCIETY: TWENTY-FIFTH ANNUAL ALBERT C. SNELL MEMORIAL LECTURE

The Rochester Ophthalmological Society will sponsor the Twenty-Fifth Annual Albert C. Snell Memorial Lecture. Clement McCulloch will be the speaker. The title of his lecture is "Diabetic Retinopathy, Where are We?" There will be an afternoon clinical session at the University of Rochester Medical Cen-

ter followed by an evening dinner and the Memorial Lecture at the Rochester Academy of Medicine. There will be a session April 11. For further information, write Primitivo D. Roca, M.D., 277 Alexander St., Rochester, NY 14607.

Tulane Medical Center: Tulane Ophthalmology Update

Tulane Medical Center will present "Tulane Ophthalmology Update" April 24-27, 1980. Registration fee is $350. For further information, write Miss Sharon A. Shirey, Assistant Director, Office of Continuing Education, Tulane Medical Center, 1430 Tulane Ave., New Orleans, LA 70112.

Miami Eye Foundation: The Miami Course in Phacoemulsification

The Miami Eye Foundation in cooperation with Bascom Palmer Eye Institute, Miami-Dade Community College, and St. Francis Hospital will present the Miami Course in Phacoemulsification, April 25-27, 1980. For further information, write Lyn Johnson, Miami Eye Foundation, 1680 Michigan Ave., Miami Beach, FL 33139.

University of Minnesota Medical School: Annual Ophthalmology Course

The Department of Ophthalmology of the University of Minnesota Medical School will present its annual course, "Current ophthalmological techniques. Lectures and demonstrations," April 28-29, 1980. For further information, write Office of Continuing Medical Education, University of Minnesota Medical School, Box 293, Mayo Memorial Bldg., 420 Delaware St. S.E., Minneapolis MN 55455.

Children's Eye Care Foundation: Research and Fellowship Support Funds in Pediatric Ophthalmology

Support for research projects in pediatric ophthalmology is available through the Children's Eye Care Foundation. Investigations must be undertaken in North America. Applications should describe the purpose of the investigation, identify the sponsors, the principal and collaborating investigators, summarize the budget and the time frames for the study as well as any other pertinent information.

Deadlines for submission of grant applications are April 30 and October 31.

Support for fellowships in pediatric ophthalmology is available through The Children's Eye Care Foundation. Training must be conducted in North America but traineeship eligibility is not limited to U.S. or Canadian citizens. Stipends are $10,000 per annum.

Priority consideration will be given to fellows who seek support for additional training after completion of a one year fellowship program in pediatric ophthalmology and strabismus and to fellows who plan to pursue academic or teaching careers after completion of fellowship training. Consideration will also be given to the relative needs of the population to be served by the fellow upon completion of training.

Requests for fellowship support will be considered after notification of acceptance to a North American training program has been received by the applicant. Letters of support from the training program director and department chairman must accompany requests for fellowship support.

For further information, write Children's Eye Care Foundation, 1015 15th St., N.W., Washington, DC 20005.

Bausch and Lomb Awards Two External Disease Fellowships

Bausch and Lomb has awarded two external disease fellowships of $15,000 each for the advancement of basic corneal research. Selected to receive External Disease Fellowships for the 1979-1980 academic year were Ann Kieler and Michael Hettinger. Applications for the 1980-1981 external disease fellowships are now being accepted. The deadline for applications is March 1, 1980. For further information, write Ms. Peggy Ross, Bausch and Lomb, 1400 N. Goodman, Rochester NY 14602.

American Intra-Ocular Implant Society: New Officers 1979-1980

The newly elected officers of the American Intra-Ocular Society are: President, Miles A. Galin; Vice President, Murry K. Weber; Secretary, Kenneth J. Hoffer; and Treasurer, Henry M. Clayman.

Wills Eye Hospital: Sixth Annual Contact Lens Conference

The Sixth Annual Contact Lens Conference of Wills Eye Hospital will be held June 5-7, 1980. For further information, write Kenneth I. Michaile, M.D., 1930 Chestnut St., Philadelphia, PA 19103.

Long Island Jewish-Hillside Medical Center: A Clinical Day in Ophthalmology Topics in Uveitis and Ocular Immunology.

The Department of Ophthalmology, Long Island Jewish-Hillside Medical Center and the Health Sciences Center, State University of New York at Stony Brook, will present "A clinical Day in Ophthalmology Topics in Uveitis and Ocular Immunology," March 19, 1980. Tuition is $60. For further information, write Continuing Education Coordinator, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11042.

Personal

Manfred Spitznas

Manfred Spitznas of Essen, Germany, has been named Wasserman Professor of Ophthalmology at UCLA's Jules Stein Eye Institute.

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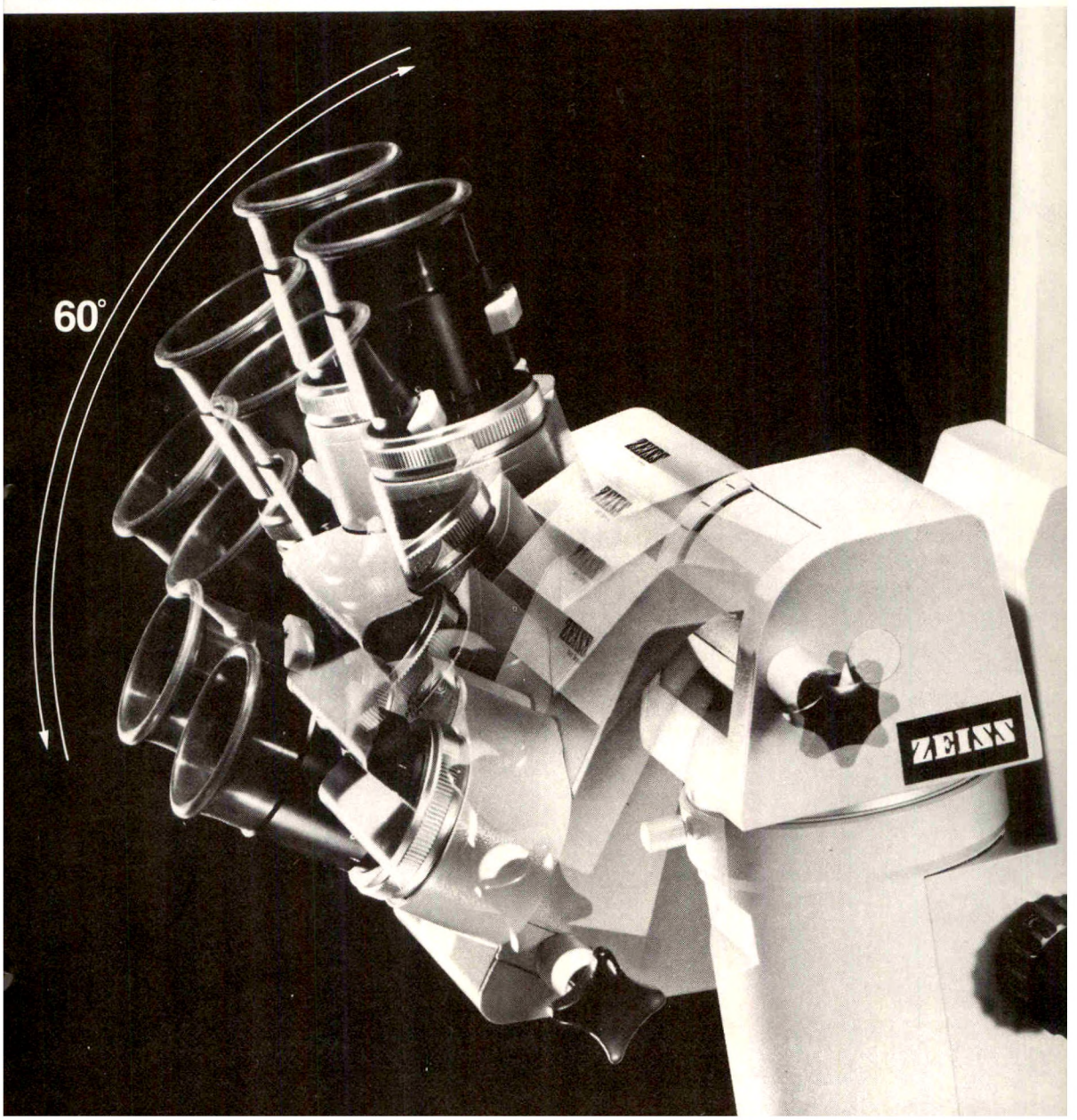

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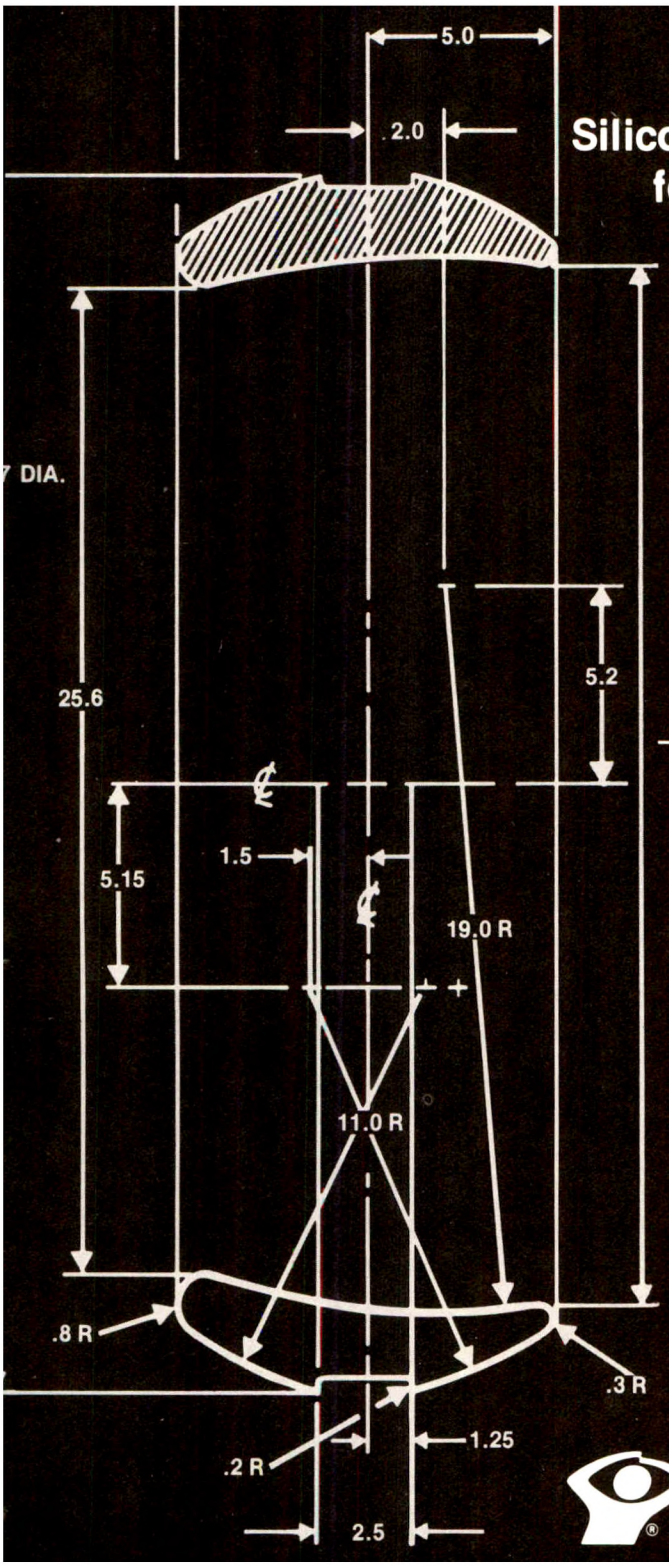

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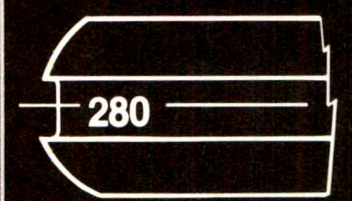

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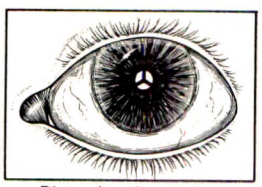
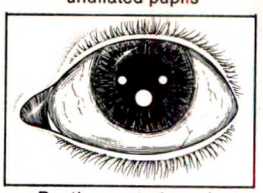
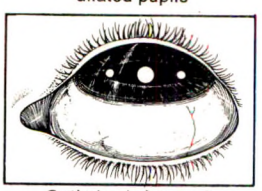


Binocular observation through small or undilated pupils



Routine posterior pole observation through dilated pupils



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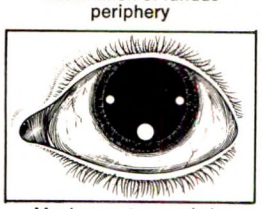

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British Journal of Ophthalmology December 1979 Vol. 63 No. 12

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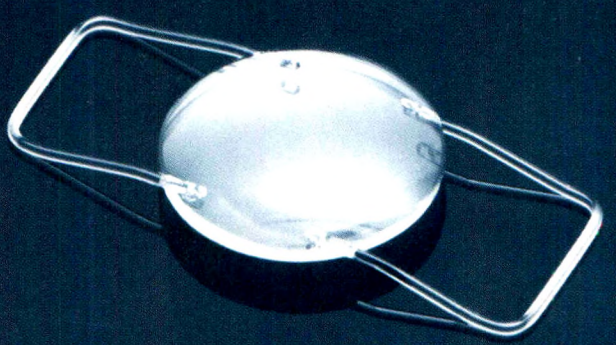

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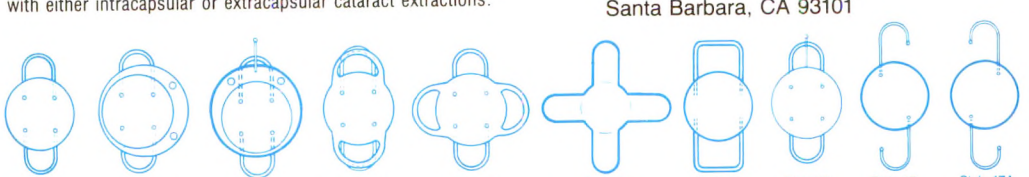

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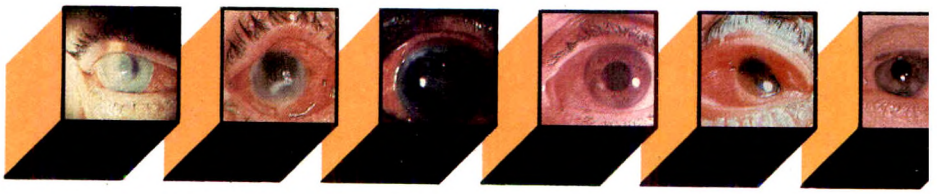

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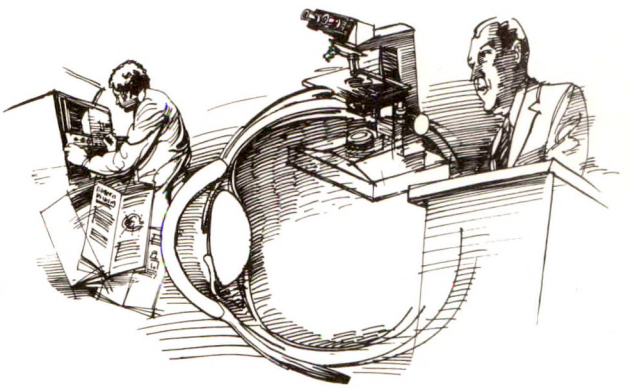

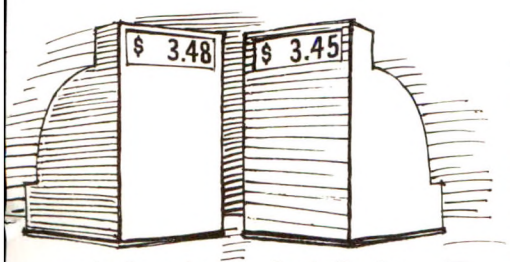

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1. Haas, J. S. and Merrill, D. L.: Am. J. Ophthal. *54*:1, 1962.
2. Linn, M. L. and Jones, L. T.: Am. J. Ophthal. *65*:1, 1968.
3. Independent Prescription Audit. Data on file at Alcon Laboratories

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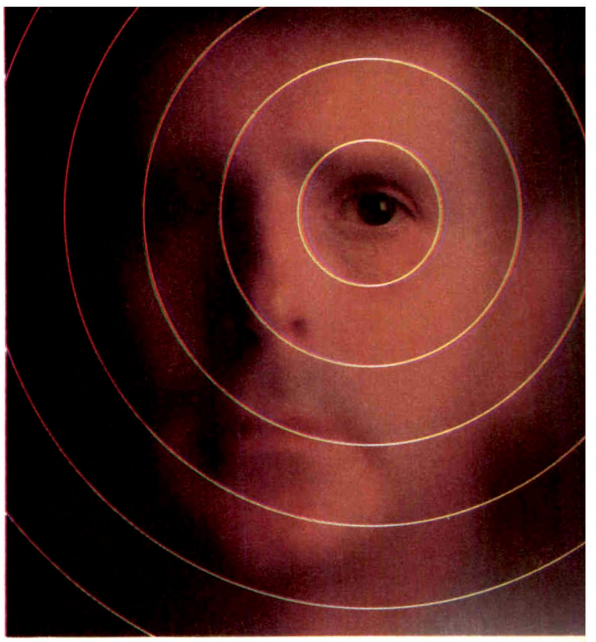

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[1] Boger, WP: Timolol: Short Term "Escape" and Long Term "Drift" ANN OPHTH 11:8(1239) 1979.
[2] Fraunfelder, FT et al: Research Leads to More Effective Ways of Administering Eyedrops JAMA 236: 21 Nov 22 1978.

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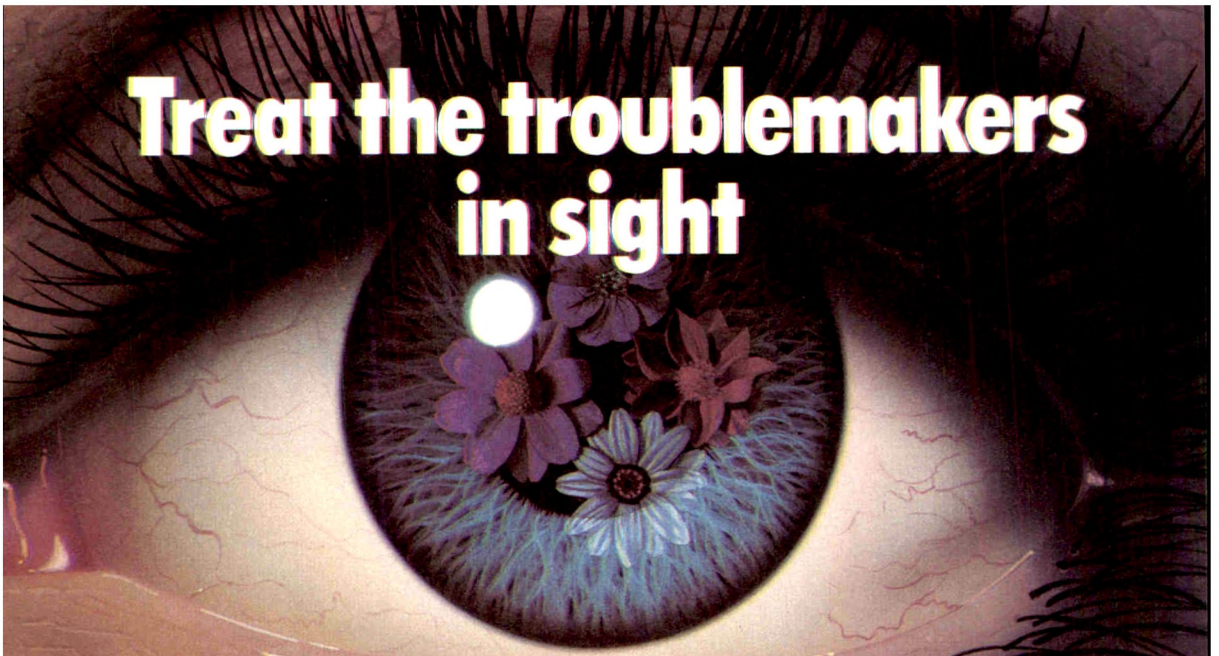

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DESCRIPTION—Contains: medrysone 1.0% with: Liquifilm (polyvinyl alcohol) 1.4%. **INDICATIONS**—HMS (medrysone) is effective in the treatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis, and epinephrine sensitivity. **CONTRAINDICATIONS**—HMS (medrysone) is contraindicated in the following conditions: Acute superficial herpes simplex. Viral diseases of the conjunctiva and cornea. Ocular tuberculosis. Fungal diseases of the eye. Hypersensitivity to any of the components of the drug. **WARNINGS**—1. Acute purulent untreated infections of the eye may be masked, enhanced or activated by the presence of steroid medication. 2. Corneal or scleral perforation occasionally has been reported with prolonged use of topical steroids. In high dosage they have been associated with corneal thinning. 3. Prolonged use of topical steroids may increase intraocular pressure, with possible resultant glaucoma, damage to the optic nerve, and defects in visual acuity and fields of vision. However, data from 2 uncontrolled studies indicate that in patients with increased intraocular pressure and in those susceptible to a rise in intraocular pressure upon application of topical steroids, there is less effect on pressure with HMS than with dexamethasone or betamethasone. 4. Prolonged use of topical corticosteroids may rarely be associated with development of posterior subcapsular cataracts. 5. Systemic absorption and systemic side effects may result with the use of topical steroids. 6. HMS® (medrysone) is not recommended for use in iritis and uveitis as its therapeutic effectiveness has not been demonstrated in these conditions. 7. Steroid medication in the presence of stromal herpes simplex requires great caution; frequent slit lamp microscopy is suggested. 8. Prolonged use may aid in the establishment of secondary ocular infections from fungi and viruses liberated from ocular tissue. **Use in Pregnancy:** The use of topical steroids in pregnancy should be limited to conditions serious enough to warrant such treatment, so that possible risk to the fetus may be justified by the expected benefit to the mother. **PRECAUTIONS**—With prolonged use of HMS (medrysone) the intraocular pressure and lens should be examined periodically. In persistent corneal ulceration where a steroid has been used, or is in use, fungal infection should be suspected. **ADVERSE REACTIONS**—Occasional transient stinging and burning may occur on instillation.

References:
1. Dorsch, W. and Thygeson, P. The clinical efficacy of medrysone, a new ophthalmic steroid. Am J Ophthalmol 65(1):74-75, 1968. 2. Thorson, J.C. and Eriksen, S.P. Anti-inflammatory properties of medrysone in external ocular inflammations. Am J Ophthalmol 71(4):844-846, 1971. 3. Bedrossian, R.H. and Eriksen, S.P. The treatment of ocular inflammation with medrysone. Arch Ophthalmol 81:184-191, 1969.

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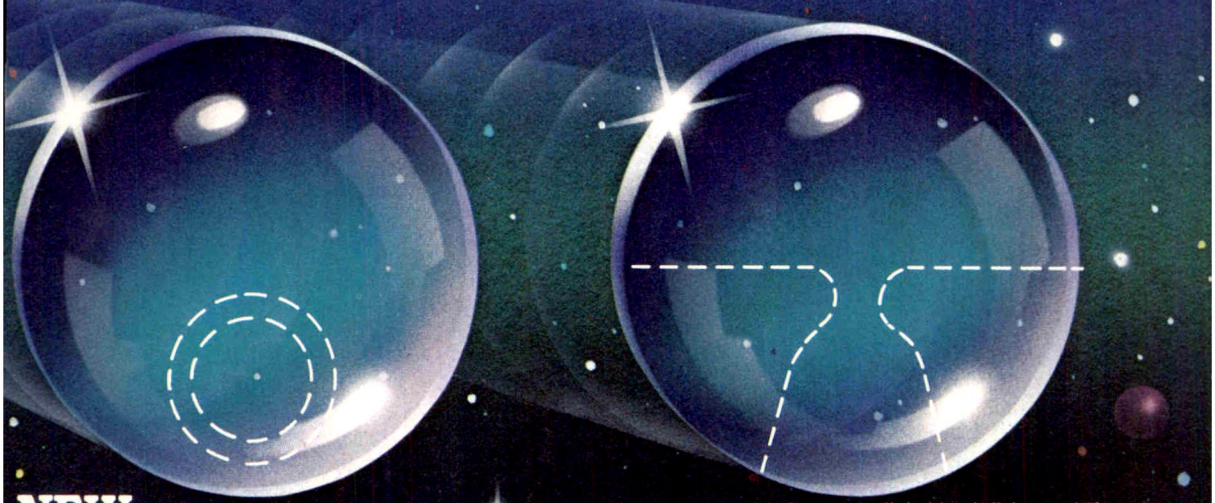

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References: 1. Data on file, American Optical Corp.
2. Wittenberg S: Field study of a new progressive addition lens. *J Am Optom Assoc* 49:1013-1021, September 1978.

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VICRYL*
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Coated VICRYL*
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SYNTHETIC ABSORBABLE SUTURE

DESCRIPTION
VICRYL (polyglactin 910) synthetic absorbable suture is prepared from a copolymer of glycolide and lactide. These substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)_m(C_3H_4O_2)_n$

Coated VICRYL synthetic absorbable suture is prepared by coating the VICRYL (polyglactin 910) suture material with a mixture composed of equal parts of a copolymer of glycolide and lactide (polyglactin 370) and calcium stearate.

These sutures are sterile, inert, nonantigenic, nonpyrogenic, and elicit only a mild tissue reaction during absorption. The braided and monofilament sutures are colored violet to enhance visibility in tissue. The braided suture is also available undyed (natural).

VICRYL and Coated VICRYL sutures differ from U.S.P. maximum diameter requirements by less than 0.05mm.

ACTIONS
Two important characteristics describe the *in vivo* behavior of absorbable sutures: first, tensile strength retention, and second, the absorption rate (loss of mass).

Subcutaneous tissue implantation studies of both VICRYL and Coated VICRYL suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its orginal strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

INDICATIONS
VICRYL and Coated VICRYL synthetic absorbable sutures are intended for use as absorbable sutures or ligatures.

CONTRAINDICATIONS
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

WARNINGS
The safety and effectiveness of VICRYL (polyglactin 910) and Coated VICRYL sutures in neural tissue and in cardiovascular tissue have not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize.

PRECAUTIONS
The VICRYL suture knots must be properly placed to be secure. Place the first throw in precise position for the final knot, using a double loop; tie the second throw square, using horizontal tension; additional throws are advisable.

Coated VICRYL sutures, which are treated to enhance handling characteristics, require the standard surgical technique of flat and square ties with additional throws if indicated by surgical circumstance and the experience of the surgeon.

Skin and conjunctival sutures remaining in place longer than 7 days may cause localized irritation and should be removed as indicated.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

ADVERSE REACTIONS
Reactions reported in clinical trials which may have been suture related have been minimal. These include skin redness and induration, rare instances of hemorrhage, anastomotic leakage, wound separation in the eye, and abscesses.

DOSAGE AND ADMINISTRATION
Use as required per surgical procedure.

HOW SUPPLIED
VICRYL sutures are available sterile as braided dyed (violet) strands in sizes 9-0 thru 3 (metric size 0.3—6) and undyed (natural) strands in sizes 8-0 thru 3 (metric size 0.4—6), in a variety of lengths, with or without needles, and on LIGAPAK ligating reels. VICRYL sutures, monofilament, dyed (violet) are available in sizes 10-0 (metric size 0.2) and 9-0 (metric size 0.3), in a variety of lengths with needles.

Coated VICRYL sutures are available sterile, as braided dyed (violet) and undyed (natural) strands in sizes 8-0 thru 2 (metric size 0.4—5), in a variety of lengths, with or without needles, and on LIGAPAK ligating reels.

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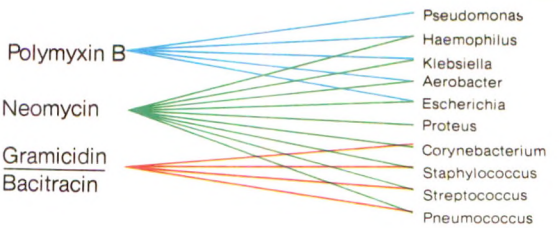

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See adjacent page for brief prescribing information.

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Brief Disclosure below applies to the solution and ointment.

INDICATIONS: For the short-term treatment of superficial external ocular infections caused by organisms susceptible to one or more of the antibiotics contained therein.

CONTRAINDICATIONS: Contraindicated in those persons who have shown sensitivity to any of the components.

WARNINGS: Prolonged use may result in overgrowth of nonsusceptible organisms. Ophthalmic Ointment may retard corneal healing.

PRECAUTIONS: Culture and susceptibility testing should be performed during treatment.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Complete literature available on request from Professional Services Dept. PML.

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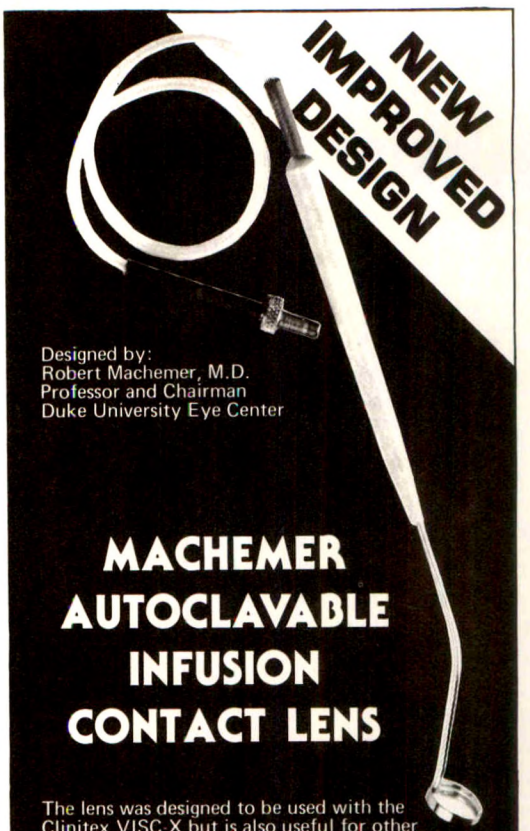

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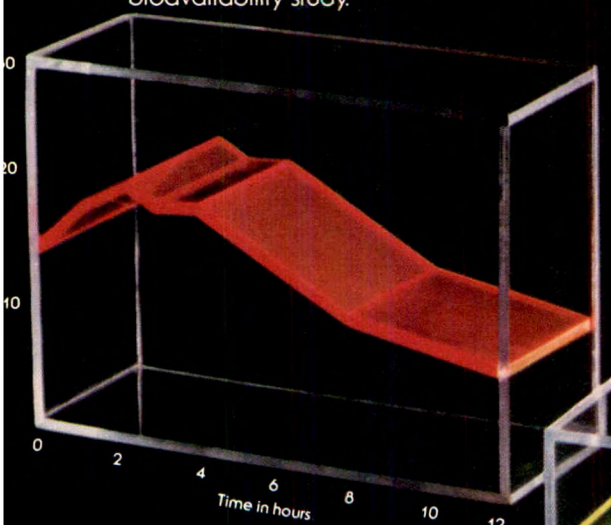

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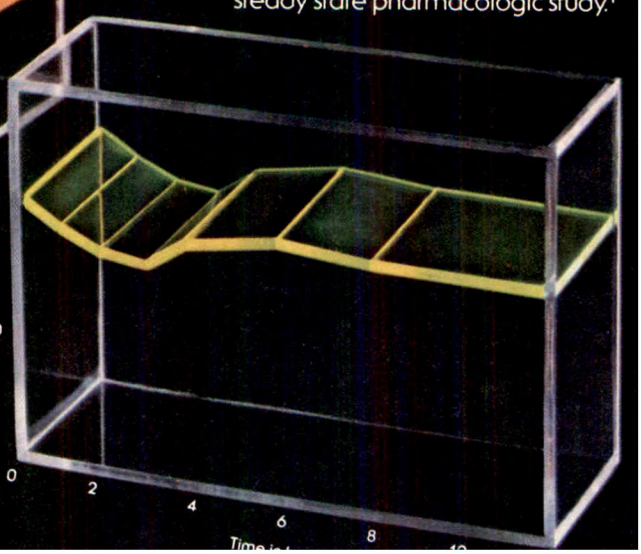

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1. Foster TS, Kielar RA: Sc Exhibit, Ann Meeting, Am Acad Ophthalmology & Otolaryngology, Kansas City, Mo, Oct 22-26, 1978.
2. Lichter PR, et al: *Am. J. Ophthalmology* 85:495, 1978.

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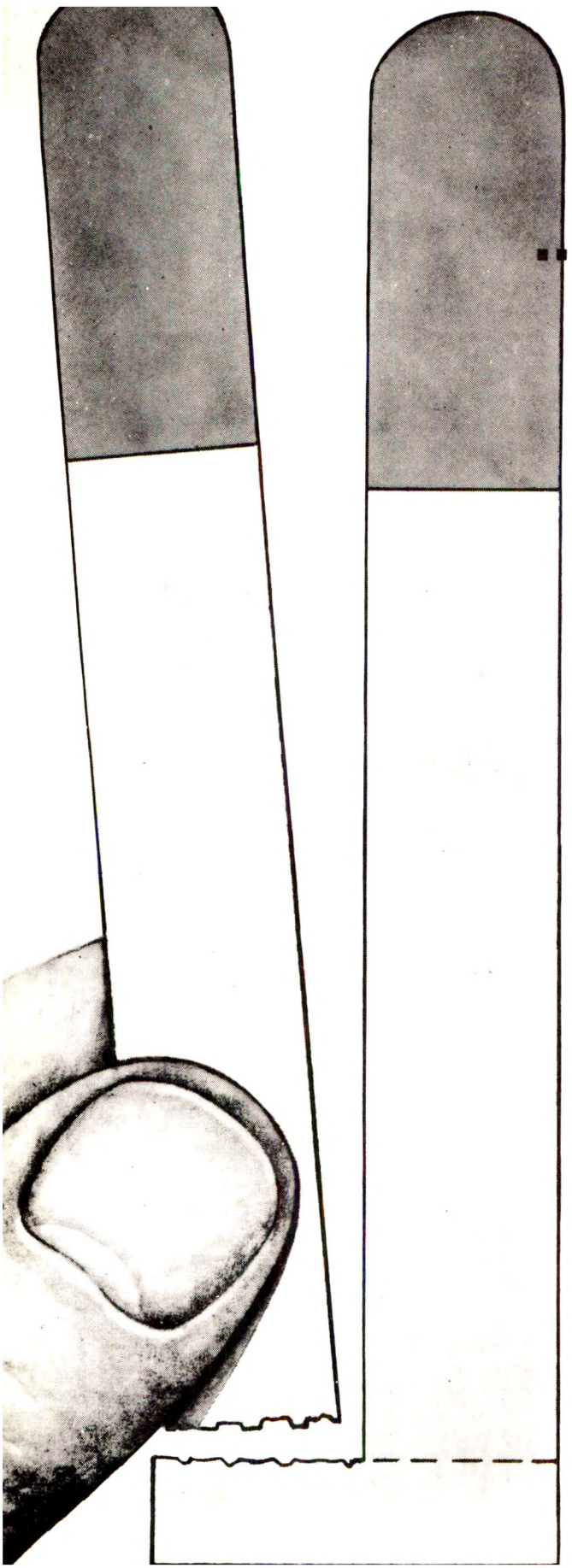

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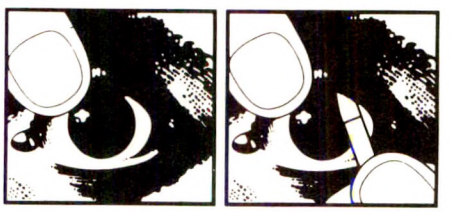

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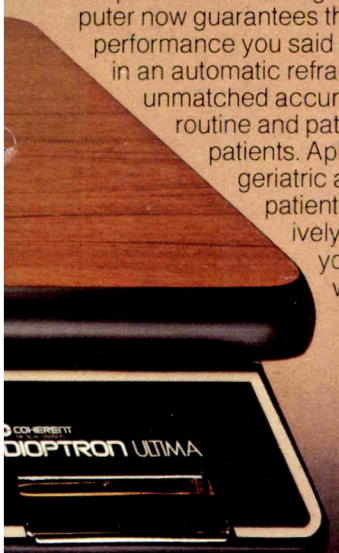

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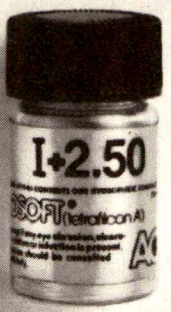

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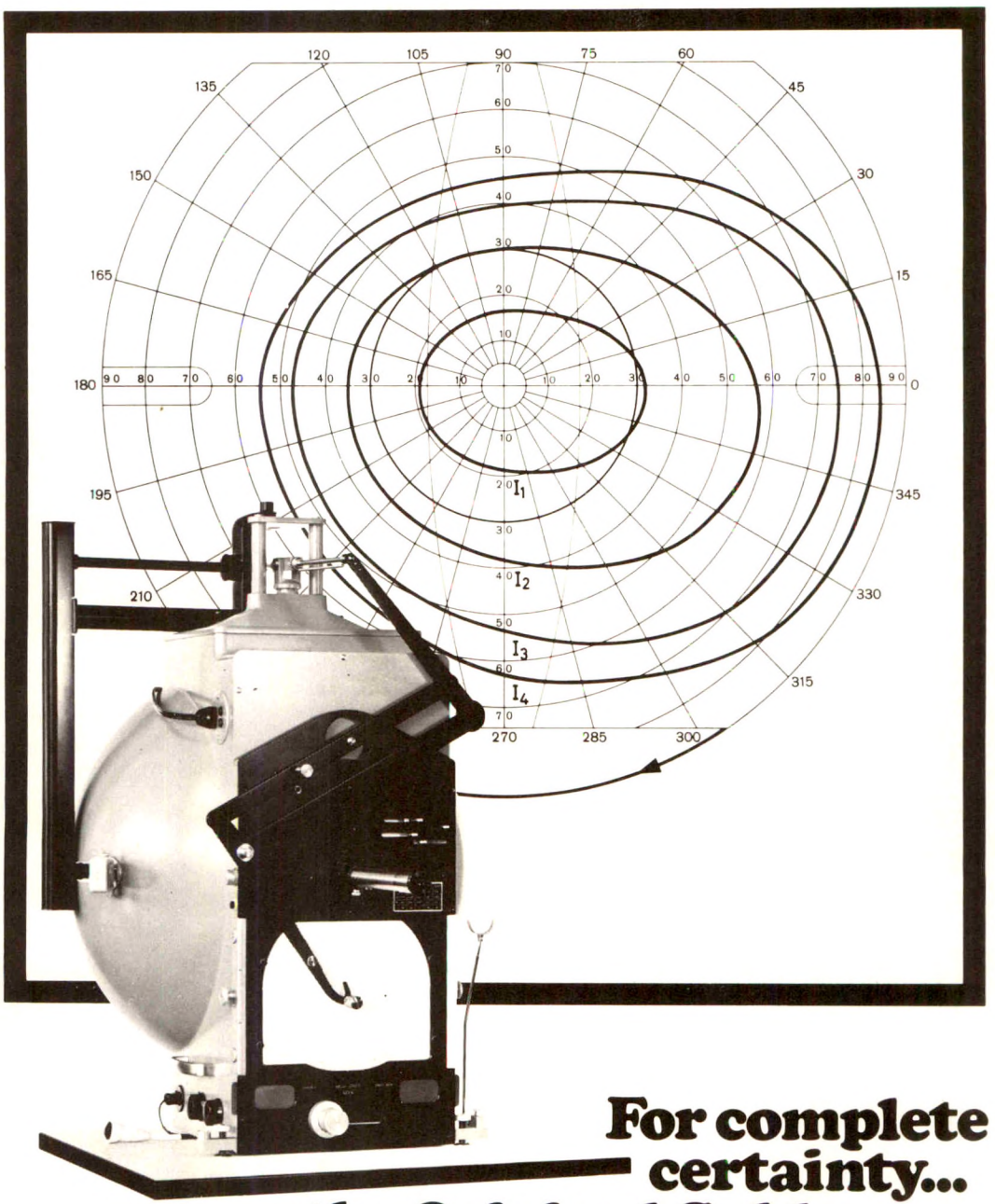

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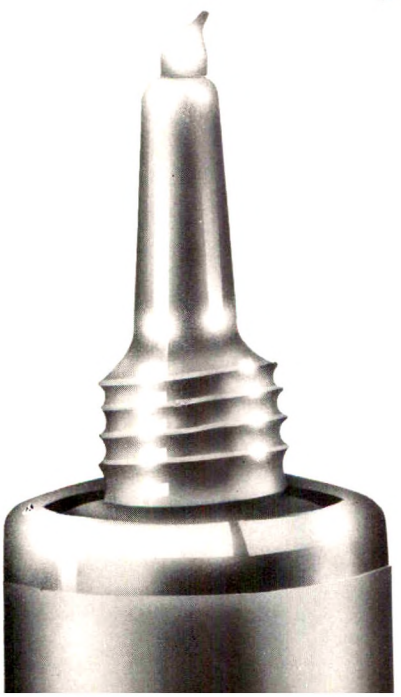

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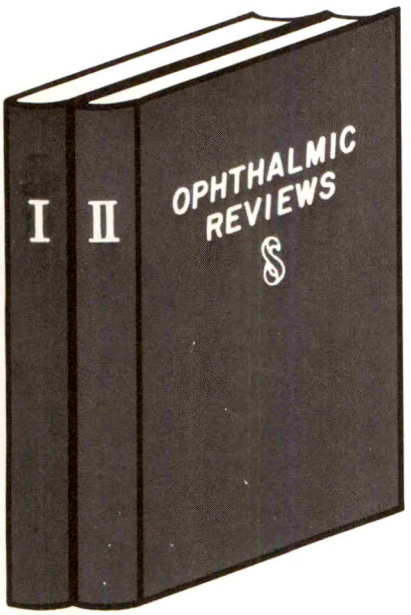

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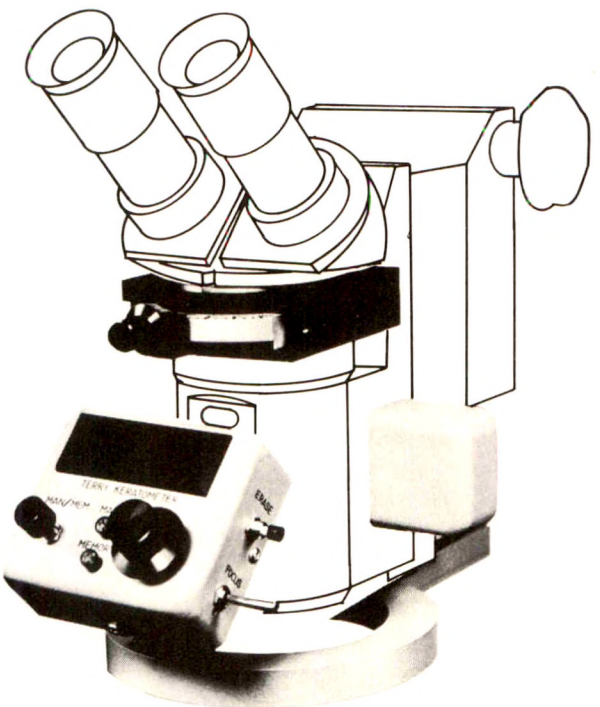

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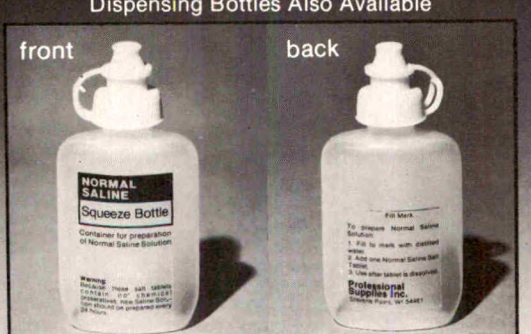

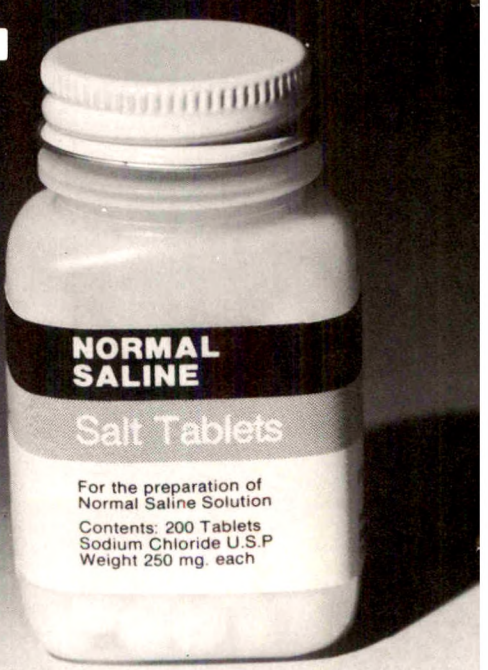

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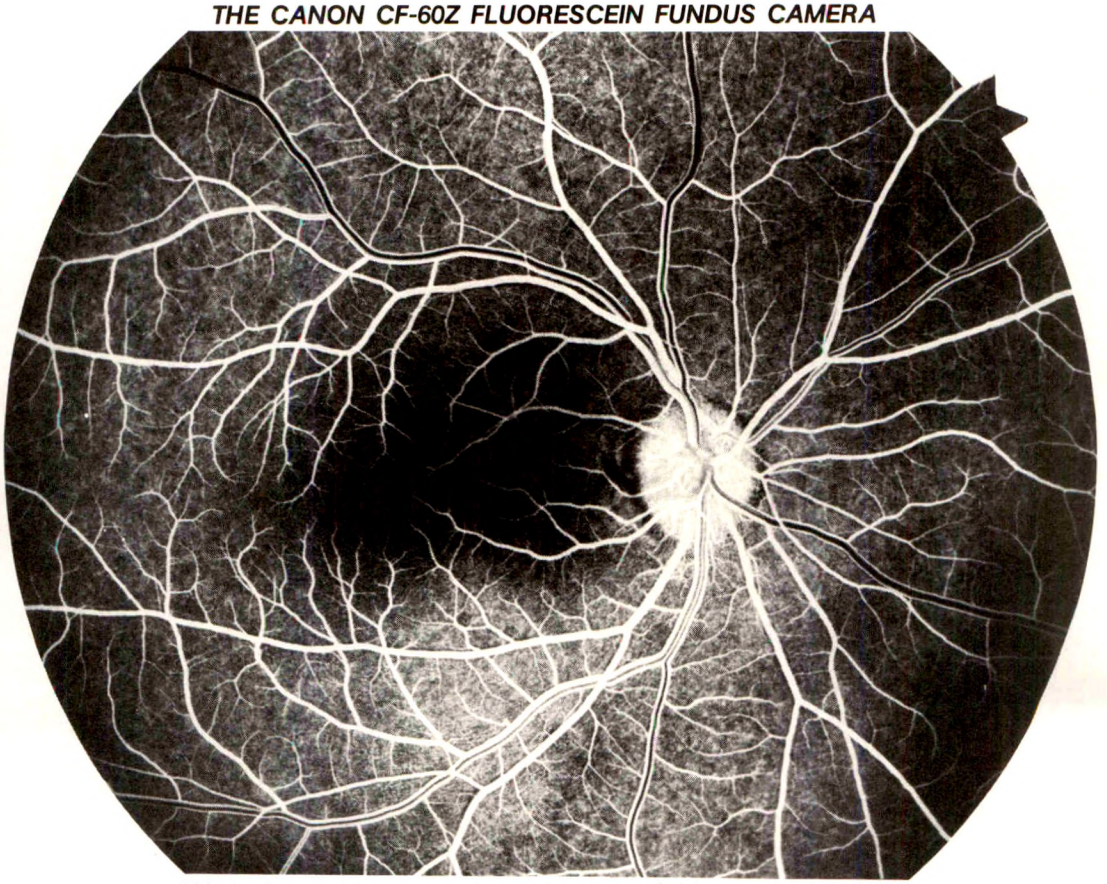

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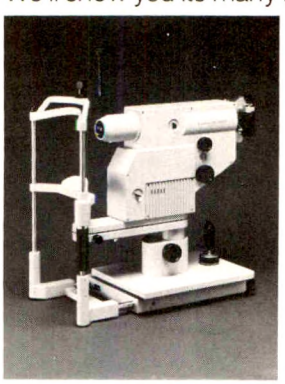

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Description. Vira-A (vidarabine, adenine arabinoside, or Ara-A) is an antiviral drug for topical ophthalmic administration. The chemical name is 9-β-D-arabinofuranosyladenine. Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

Clinical Pharmacology. Vira-A is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Except for Rhabdovirus and Oncornavirus, Vira-A does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

The antiviral mechanism of action has not been established. Vira-A appears to interfere with the early steps of viral DNA synthesis. Vira-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of Vira-A. Because of the low solubility of Vira-A, trace amounts of both Vira-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of Vira-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, Vira-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, Vira-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit.

Indications and Usage. Vira-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. Vira-A is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions to idoxuridine have occurred. The effectiveness of Vira-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous Vira-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone, have been administered concurrently with Vira-A Ophthalmic Ointment, 3%, without an increase in adverse reactions.

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If Vira-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

Vira-A is not effective against RNA virus or adenoviral ocular infections. Vira-A is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Contraindication. Vira-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. ***Use in Pregnancy:*** Vira-A (vidarabine) parenterally is teratogenic in rats and rabbits. Ten percent Vira-A ointment applied to 10% of the body surface during organogenesis induced fetal abnormalities in rabbits. When 10% Vira-A ointment was applied to 2 to 3% of the body surface of rabbits, no fetal abnormalities were found. This dose greatly exceeds the total recommended ophthalmic dose in humans. The possibility of embryonic or fetal damage in pregnant women receiving Vira-A (vidarabine ophthalmic ointment), 3%, is remote. The topical ophthalmic dose is small, and the drug relatively insoluble. Its ocular penetration is very low. However, a safe dose for a human embryo or fetus has not been established. Consequently, Vira-A should be used only when clearly indicated.

It is not known whether Vira-A is excreted in human milk. As a general rule, because many drugs are excreted in human milk, nursing should not be undertaken while a patient is under treatment. However, excretion of vidarabine in breast milk is unlikely because Vira-A is rapidly deaminated in the gastrointestinal tract.

Mutagenic Potential: Results of *in vitro* experiments indicate that vidarabine can be incorporated into mammalian DNA and can induce mutation in mammalian cells (mouse L5178Y cell line). Thus far, *in vivo* studies have not been as conclusive, but there is some evidence (dominant lethal assay in mice) that vidarabine may be capable of producing mutagenic effects in male germ cells.

It has also been reported that vidarabine causes chromosome breaks and gaps when added to human leukocytes *in vitro*. While the significance of these effects in terms of mutagenicity is not fully understood, there is a well-known correlation between the ability of various agents to produce such effects and their ability to produce heritable genetic damage.

Oncogenic Potential: Chronic parenteral (IM) studies of vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant increase in liver tumor incidence among the vidarabine-treated females. In the same study, some vidarabine-treated male mice developed kidney neoplasia. No renal tumors were found in the vehicle-treated control mice or the vidarabine-treated female mice.

In the rat study, intestinal, testicular, and thyroid neoplasia occurred with greater frequency among the vidarabine-treated animals than in the vehicle-treated controls. The increases in thyroid adenoma incidence in the high-dose (50 mg/kg) males and the low-dose (30 mg/kg) females were statistically significant.

Hepatic megalocytosis, associated with vidarabine treatment, has been found in short- and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.

The recommended frequency and duration of administration should not be exceeded (see Dosage and Administration).

Precautions. The diagnosis of keratoconjunctivitis due to Herpes simplex virus should be established clinically prior to prescribing Vira-A Ophthalmic Ointment, 3%.

Patients should be forewarned that Vira-A Ophthalmic Ointment, 3%, like any ophthalmic ointment, may produce a temporary visual haze.

Although viral resistance to Vira-A has not been observed, this possibility may exist.

Adverse Reactions. Lacrimation, foreign-body sensation, conjunctival injection, burning, irritation, superficial punctate keratitis, pain, photophobia, punctal occlusion, and sensitivity have been reported with Vira-A Ophthalmic Ointment, 3%. The following have also been reported but appear disease-related: uveitis, stromal edema, secondary glaucoma, trophic defects, corneal vascularization, and hyphema.

Overdosage. Acute massive overdosage by oral ingestion of the ophthalmic ointment has not occurred. However, the rapid deamination to arabinosylhypoxanthine should preclude any difficulty. The oral LD_{50} for vidarabine is greater than 5,020 mg/kg in mice and rats. No untoward effects should result from ingestion of the entire contents of a tube.

Overdosage by ocular instillation is unlikely because any excess should be quickly expelled from the conjunctival sac. Too frequent administration should be avoided.

Dosage and Administration. Administer approximately one half inch of Vira-A Ophthalmic Ointment, 3%, into the lower conjunctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or complete re-epithelialization has not occurred by 21 days, other forms of therapy should be considered. Some severe cases may require longer treatment.

After re-epithelialization has occurred, treatment for an additional seven days at a reduced dosage (such as twice daily) is recommended in order to prevent recurrence.

How Supplied. N 0071-3677-07 (Stock 18-1677-139)

Vira-A Ophthalmic Ointment, 3%, is supplied sterile in ophthalmic ointment tubes of 3.5 g. The base is a 60:40 mixture of solid and liquid petrolatum. **UK**

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PD-JA-2320-1-P (5-78)

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Not only as effective as IDU in treating Herpes simplex virus keratitis...

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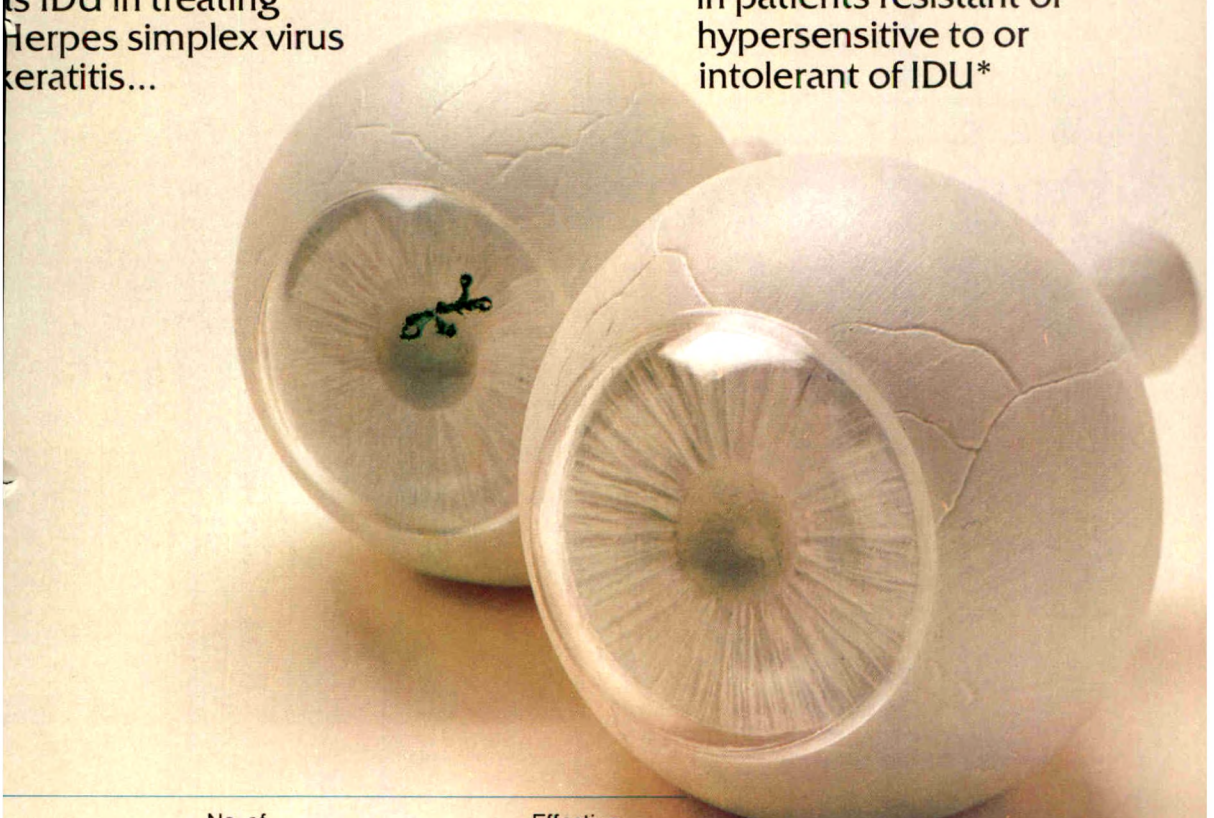

Clinical Evidence	No. of Subjects	Description	Effective Response
Vira-A Controlled Trials	81	Previously untreated	70 subjects **(86%)**
Vira-A Uncontrolled Trials	142	75% had been resistant or hypersensitive to IDU	101 subjects **(71%)**

NOTE: In the controlled and uncontrolled trials, 70 and 101 subjects, respectively, re-epithelialized at the end of three weeks on Vira-A.

*Data on file, Medical Department, Parke-Davis

Vira-A is preservative-free.

Please see prescribing information on preceding page.

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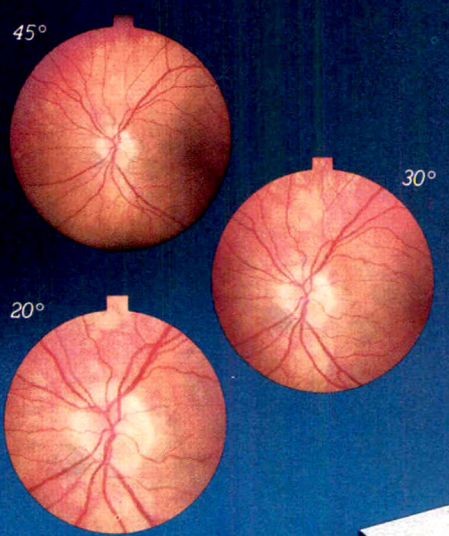

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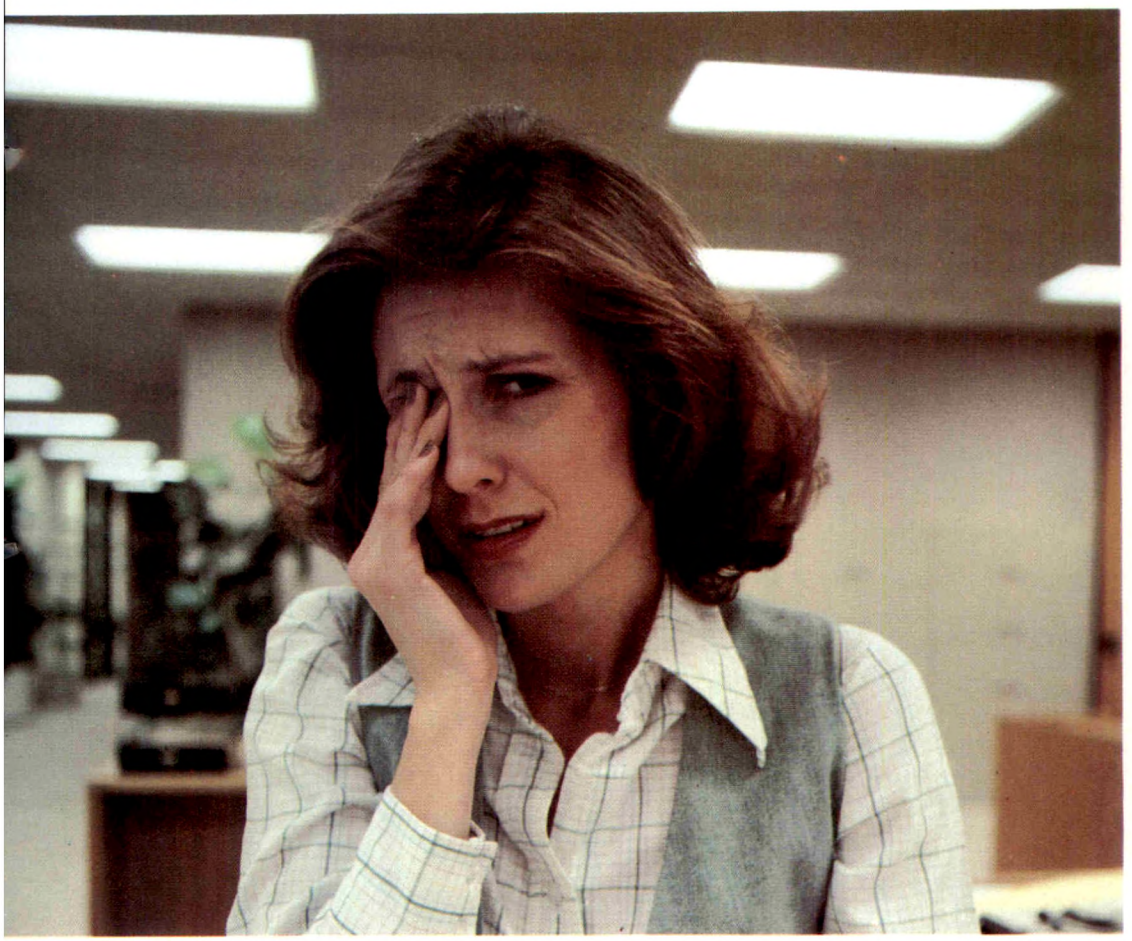

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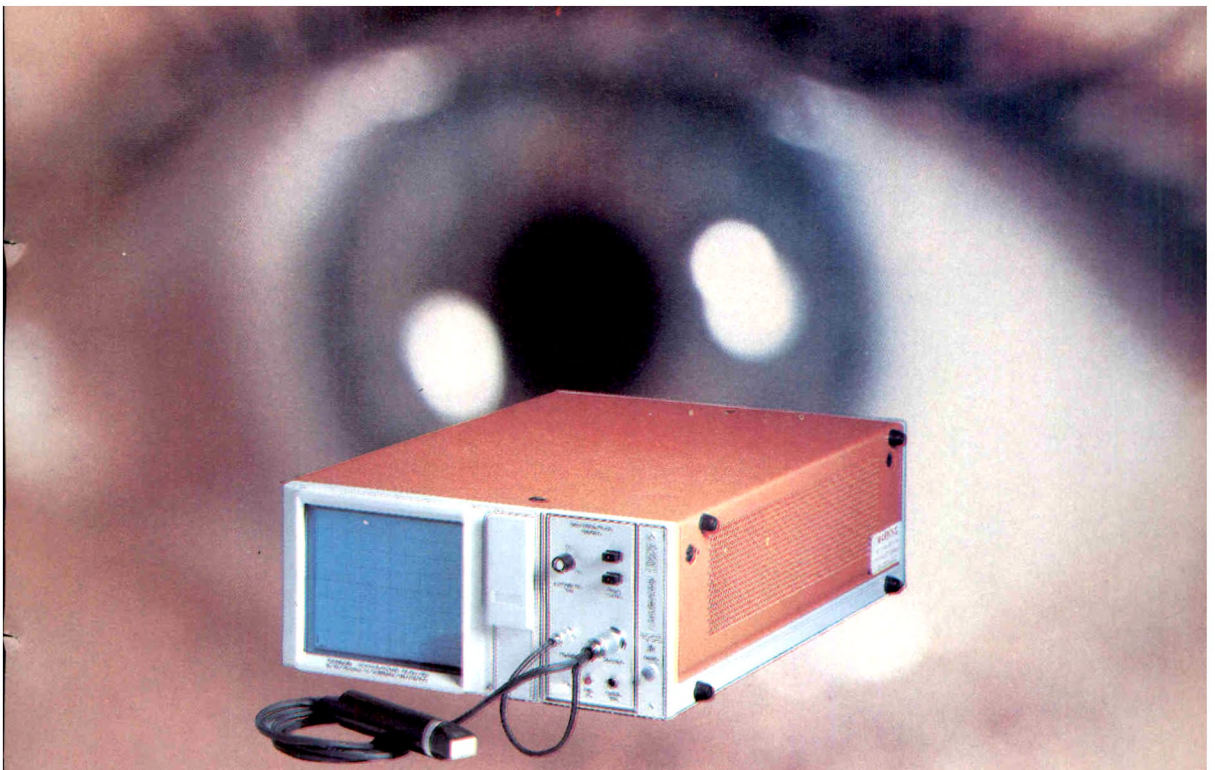

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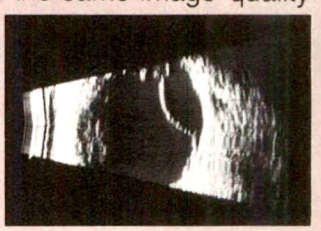

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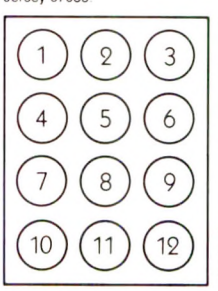

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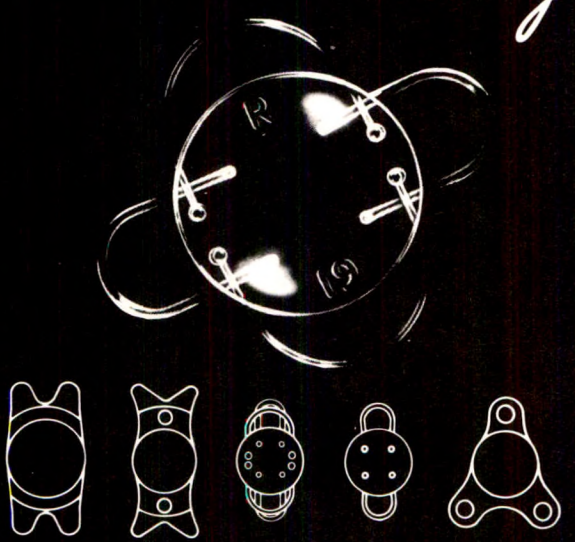

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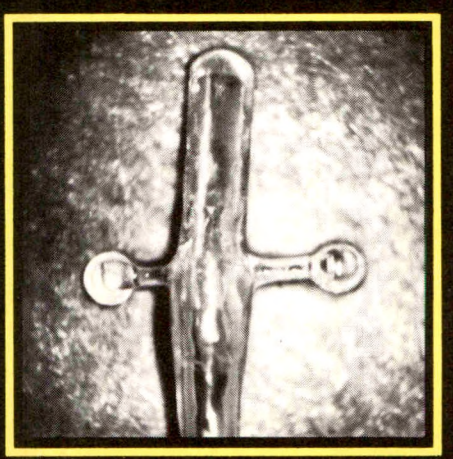

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Ref: Krupin, Theodore, M.D., "Valve Implant in Neovascular Glaucoma," Glaucoma Symposium, San Francisco, Nov. 6, 1979

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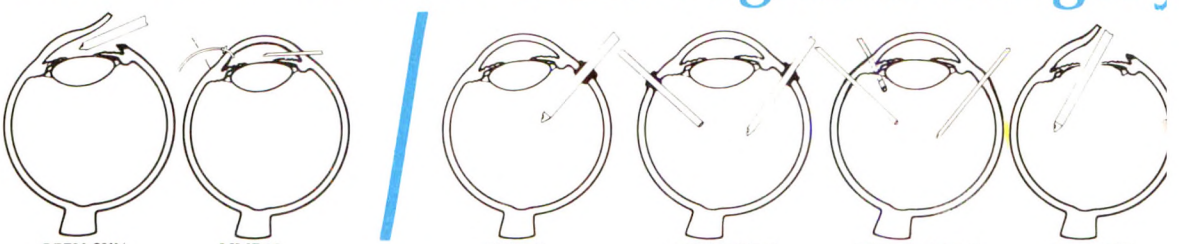

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1.65 or 2.3 mm

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1.65 mm

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3 Port System
1 mm

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of tip sizes

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- **Automatic or Manual Suction/Reflux**
- **Micro-Tips: 1 mm**
  Mini-Tips: 1.65 mm
  Lentectomy Tips: 2.3 mm

The VISC-X is a revolutionary new concept in systems for anterio posterior segment surgery. It permits the surgeon to employ a wide variety of techniques through singular or multiple incisions Using the modular building block approach, the surgeon can create a system customized for present requirements and preferences. As needs change, the VISC-X systems may be expanded to permit additional techniques and procedures.

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- Independent or concurrent cutting, suction, reflux, illumination, and bipolar bimanual diathermy
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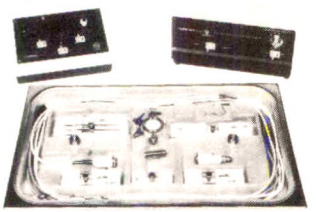

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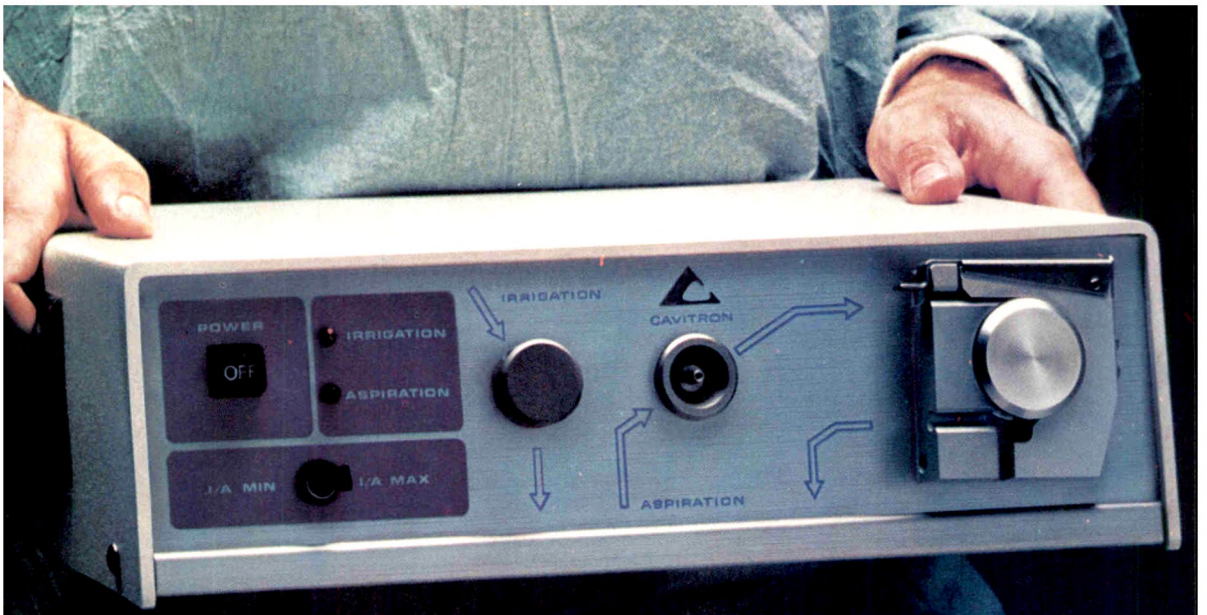

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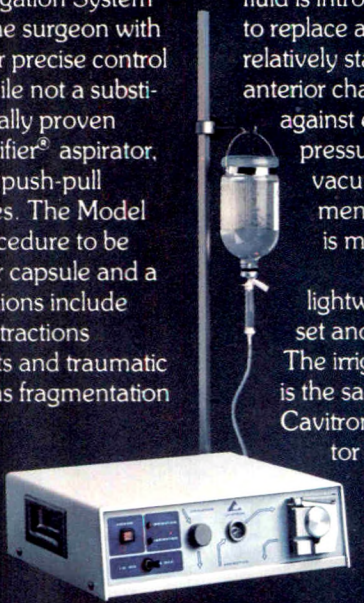
The Cavitron Extraction-Irrigation System (E.I.S.), Model 6500, provides the surgeon with a reasonably priced instrument for precise control over irrigation and aspiration. While not a substitute for the widely used and clinically proven Cavitron/Kelman® Phaco-Emulsifier® aspirator, it makes an ideal replacement for push-pull syringe or squeeze bulb techniques. The Model 6500 allows an extracapsular procedure to be performed with an intact posterior capsule and a clean posterior chamber. Applications include planned extracapsular cataract extractions preceding intraocular lens implants and traumatic and congenital cataracts when lens fragmentation may not be required.

The key to the E.I.S. is the proven vacuum control system developed by Cavitron. During the procedure, a sterile irrigating fluid is introduced into the anterior chamber to replace aspirated fluid and materials. A relatively stable pressure is maintained within the anterior chamber which provides a safeguard against excessive, rapid changes in intraocular pressure. The surgeon can select one of two vacuum levels to meet varying requirements. Time spent in the anterior chamber is minimal.



The E.I.S. consists of a portable, lightweight console, surgical handpiece set and surgeon-controlled footswitch. The irrigation/aspiration system employed is the same basic design as that used in the Cavitron/Kelman Phaco-Emulsifier aspirator for more than 200,000 surgical cases.

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5% sodium chloride sterile ophthalmic ointment and solution

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  - Sterile ophthalmic ointment
  - Sterile ophthalmic solution
- 5% sodium chloride
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- Prolonged retention on cornea
- Less burning and stinging

SOLUTION
- Addition of methylcellulose
- Added viscosity

MURO 128 OINTMENT AND SOLUTION
- Greater reduction of corneal edema
- Better patient compliance

MURO 128
(Sodium Chloride 5% Ointment)

DESCRIPTION: A sterile ophthalmic ointment of sodium chloride 5% in a base of lanolin, liquid petrolatum and white petrolatum.

MURO 128
(Sodium Chloride 5% Solution)

DESCRIPTION: A sterile ophthalmic solution of sodium chloride 5% with methylcellulose 0.9%. Also contains methylparaben 0.023% and propylparaben 0.01% as preservatives, and purified water.

INDICATIONS: As an aid for reducing edema in conditions of the cornea from various causes as bullous keratitis, keratopathy and following cataract surgery and Fuchs' endothelial-epithelial dystrophy.

CONTRAINDICATED: Hypersensitivity to any ingredient.

ADVERSE REACTION: Slight stinging sensation which is usually transient in nature.

OINTMENT DOSAGE: One or more times a day as directed by physician.

HOW SUPPLIED: As a sterile ophthalmic ointment in 3.5g tubes. Keep tightly closed—store in a cool place.

SOLUTION DOSAGE: 1 or 2 drops in affected eye(s) three times a day, or as directed by the physician.

HOW SUPPLIED: 15 ml and 30 ml plastic dropper bottles. Keep tightly closed—store in a cool place.

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription.

WARNING: For topical ophthalmic use only. Do not touch tip of tube or dropper tip to any surface since this may contaminate ointment or solution.

* Luxenberg, M.N., and Greek, K.: Reduction of Corneal Edema with topical hypertonic agents. Am. J. Ophth. 71:847, 1971.

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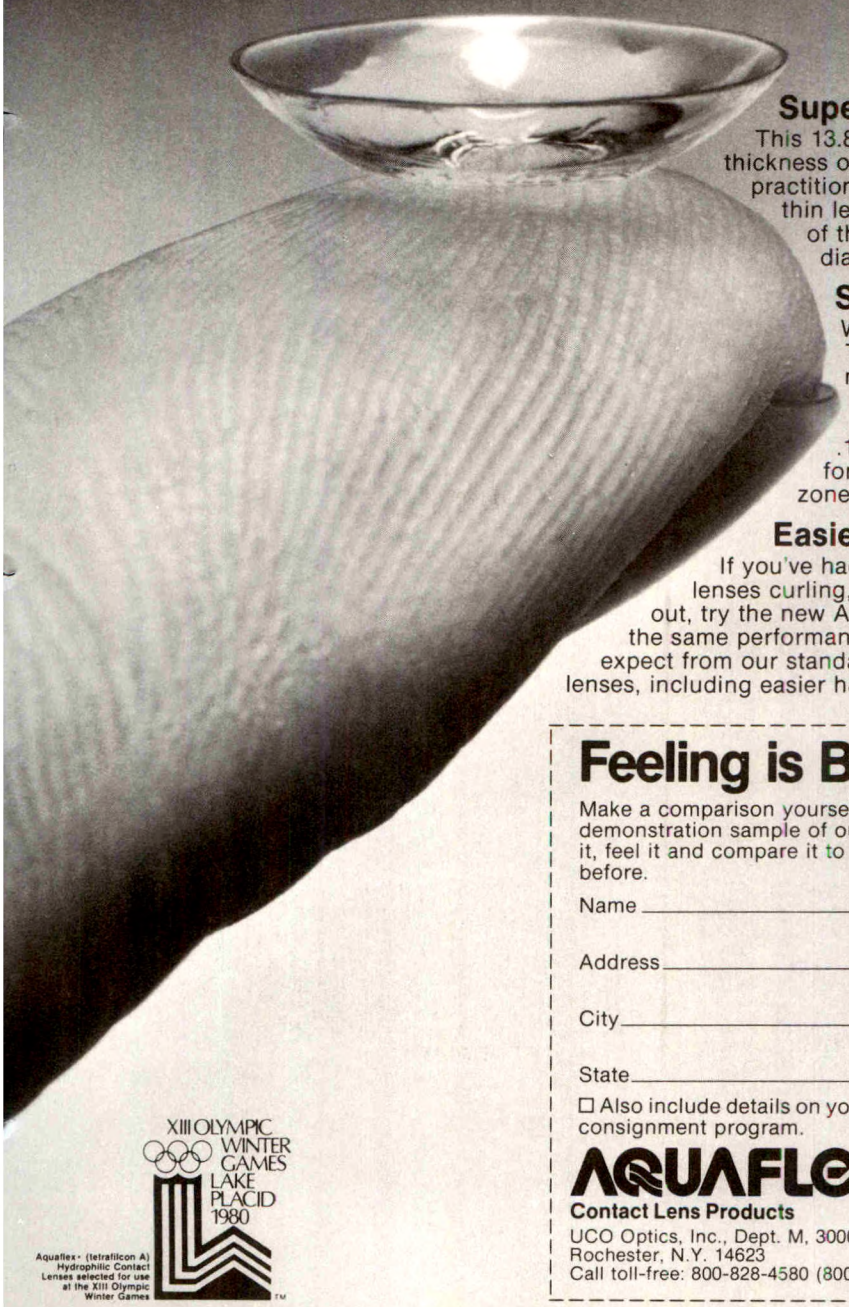

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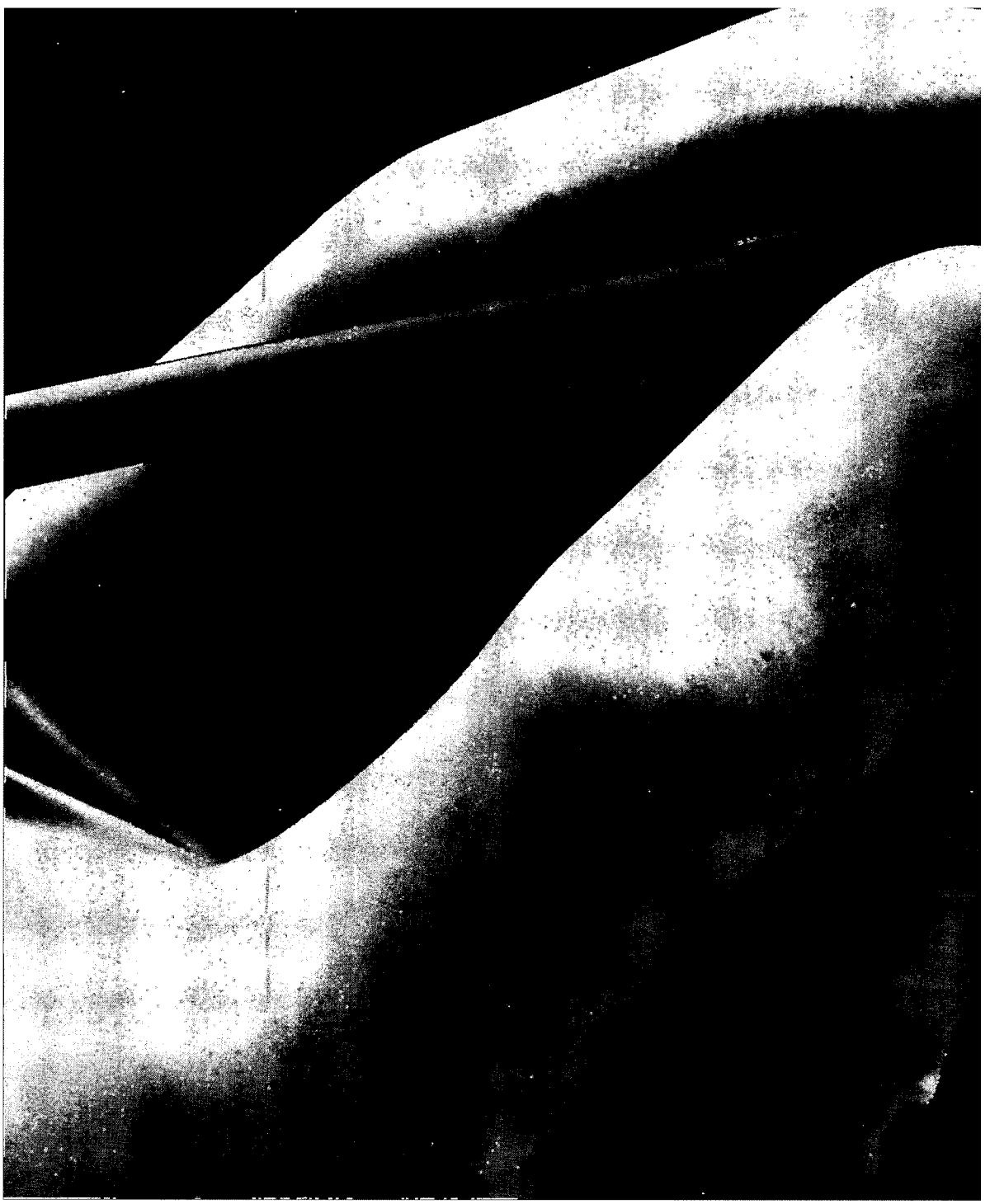

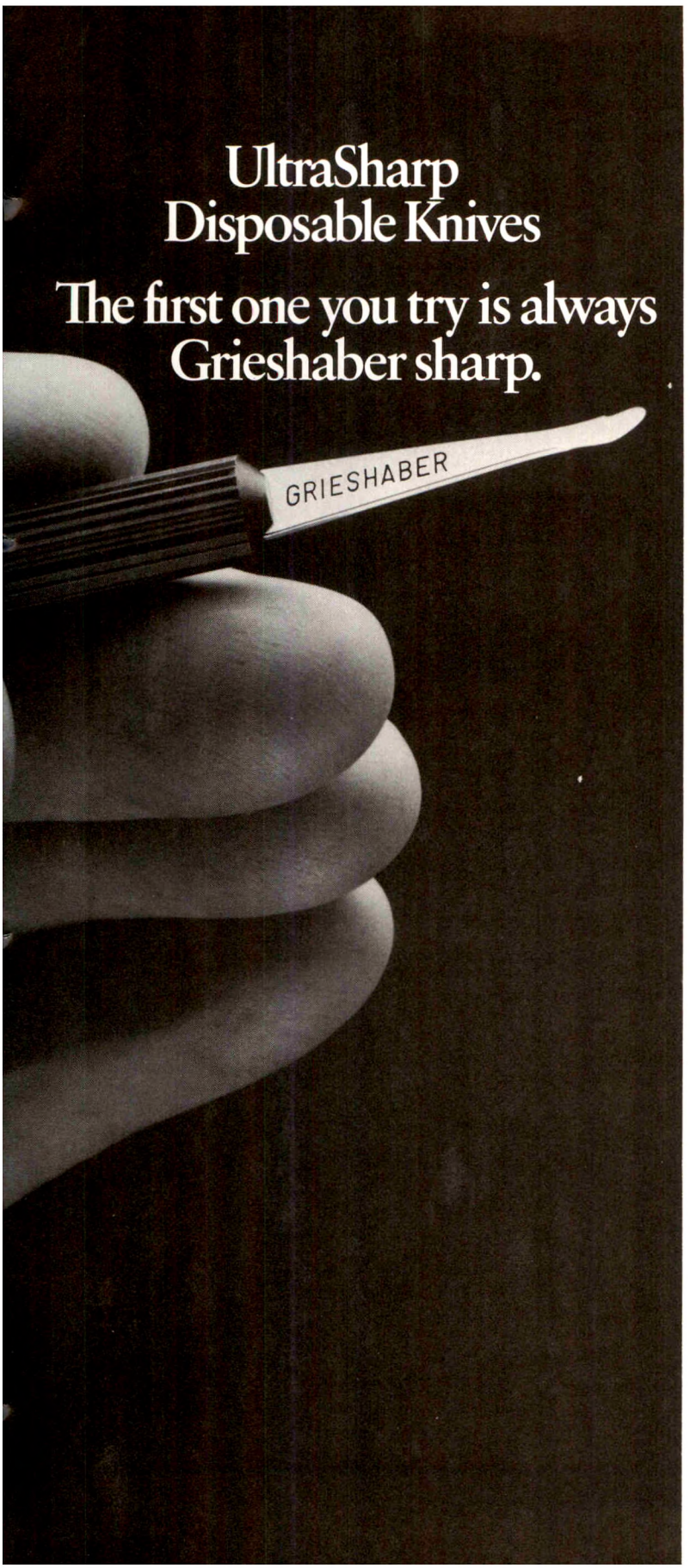

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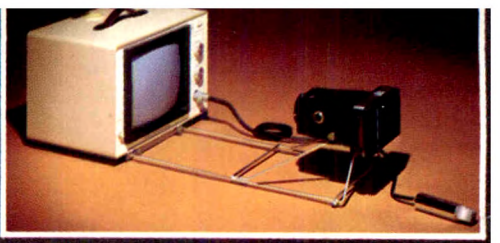

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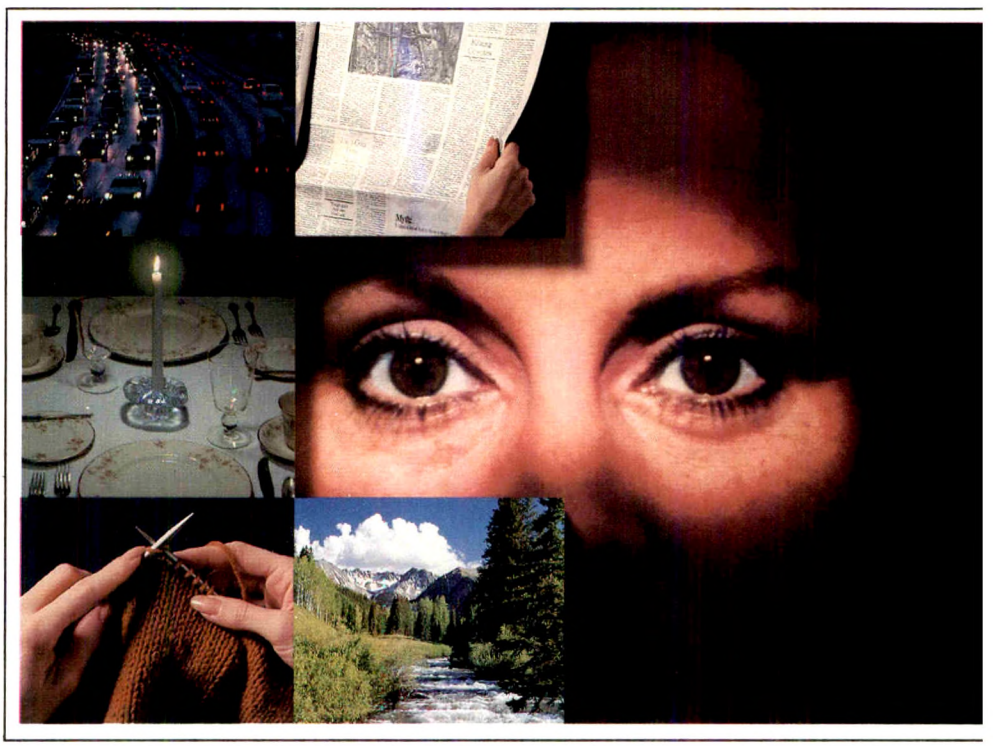
In chronic open-angle glaucoma therapy

Two good reasons to switch patients to



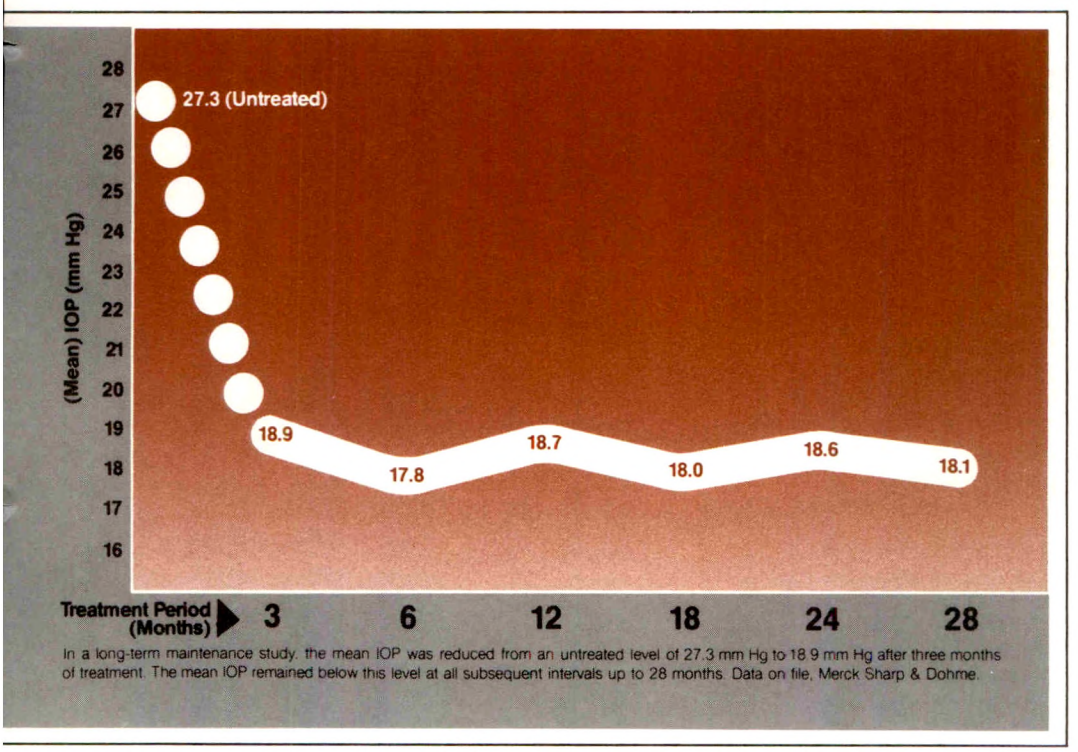
1. A better quality of life for many patients...

Patients on TIMOPTIC® (Timolol Maleate, MSD) generally do *not* experience the following therapy-limiting side effects:

change in pupil size/dimming of vision/night blindness*

TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product. Occasionally, mild ocular irritation has been reported.

Timoptic®
(TIMOLOL MALEATE | MSD)
OPHTHALMIC SOLUTION



In a long-term maintenance study, the mean IOP was reduced from an untreated level of 27.3 mm Hg to 18.9 mm Hg after three months of treatment. The mean IOP remained below this level at all subsequent intervals up to 28 months. Data on file, Merck Sharp & Dohme.

2. Efficacy maintained in long-term therapy...

- No tolerance was observed in 102 patients for 28 months
- TIMOPTIC was significantly more effective than pilocarpine or epinephrine in reducing elevated IOP*
- TIMOPTIC reduced IOP in 3 out of 4 patients*

Based on controlled multiclinic studies, evaluating over 1000 patients.

MSD
MERCK SHARP & DOHME

For a brief summary of Prescribing Information, please see following page. Copyright © 1979 by Merck & Co., Inc.

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NEW
10-ml OCUMETER®

Timoptic®
(TIMOLOL MALEATE | MSD)
OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution

a significant advance for the reduction of IOP in:

- chronic open-angle glaucoma
- aphakic glaucoma
- some patients with secondary glaucoma
- ocular hypertension
- some patients who respond inadequately to multiple antiglaucoma drug therapy

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in each eye twice a day.

How to transfer from current therapy to TIMOPTIC:
1. On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC in each eye b.i.d.

2. On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC in each eye b.i.d.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in each eye. Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in each eye.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.

℞
Timoptic
(Timolol
Maleate | MSD)
0.25%
one drop
in each eye
b.i.d.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.
PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.
Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.
Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.
ADVERSE REACTIONS: Occasionally, signs and symptoms of mild ocular irritation have been reported. Local hypersensitivity reactions, including localized and generalized rash, have occurred rarely.

Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Rarely, episodes of acute bronchospasm have been reported in patients with bronchospastic disease (see PRECAUTIONS).
Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studied in patients wearing lenses made with materials other than PMMA.
HOW SUPPLIED:
TIMOPTIC Ophthalmic Solution, 0.25%
TIMOPTIC Ophthalmic Solution, 0.5%
Both are available in 5-ml and 10-ml plastic OCUMETER® Ophthalmic Dispensers with a controlled drop tip.
J9TM08 (DC7046008)

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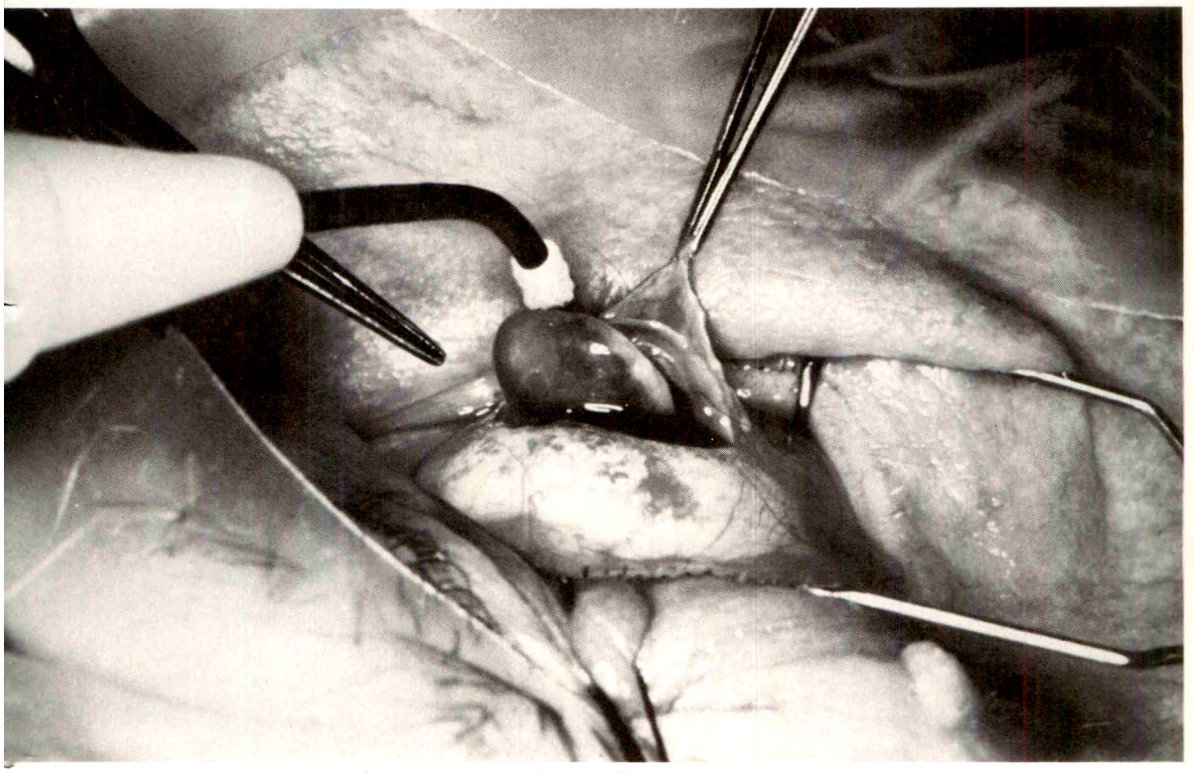
KRYmed delivers



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M. Dunn, M. D.	A. Messina, M. D.
H. Gould, M. D.	E. Wiggs, M. D.
M. Guibor, C. O.	D. Wolfley, M. D.
	and others.

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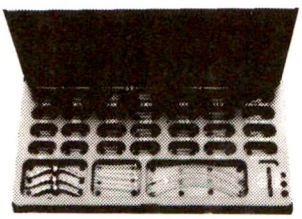

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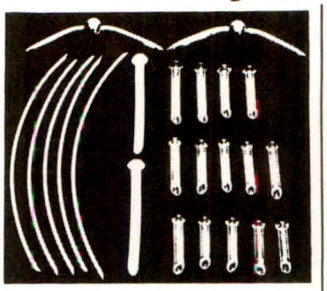

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* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
J.C. Mustarde', L.T. Jones M.D. and A. Callahan M.D., Ophthalmic Plastic Surgery---Up-To-Date, Aesculapius Publishing Company, 1970.
L.T. Jones M.D. and J.L. Wobig M.D., Surgery of the Eyelids and Lacrimal System, Aesculapius Publishing Company, 1976.

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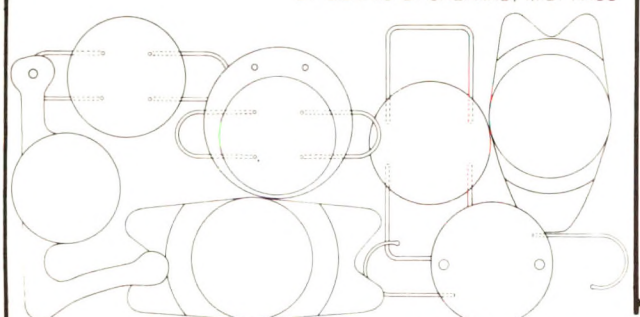
the intraocular lens manual

BY DENNIS D. SHEPARD, M.D. FACS



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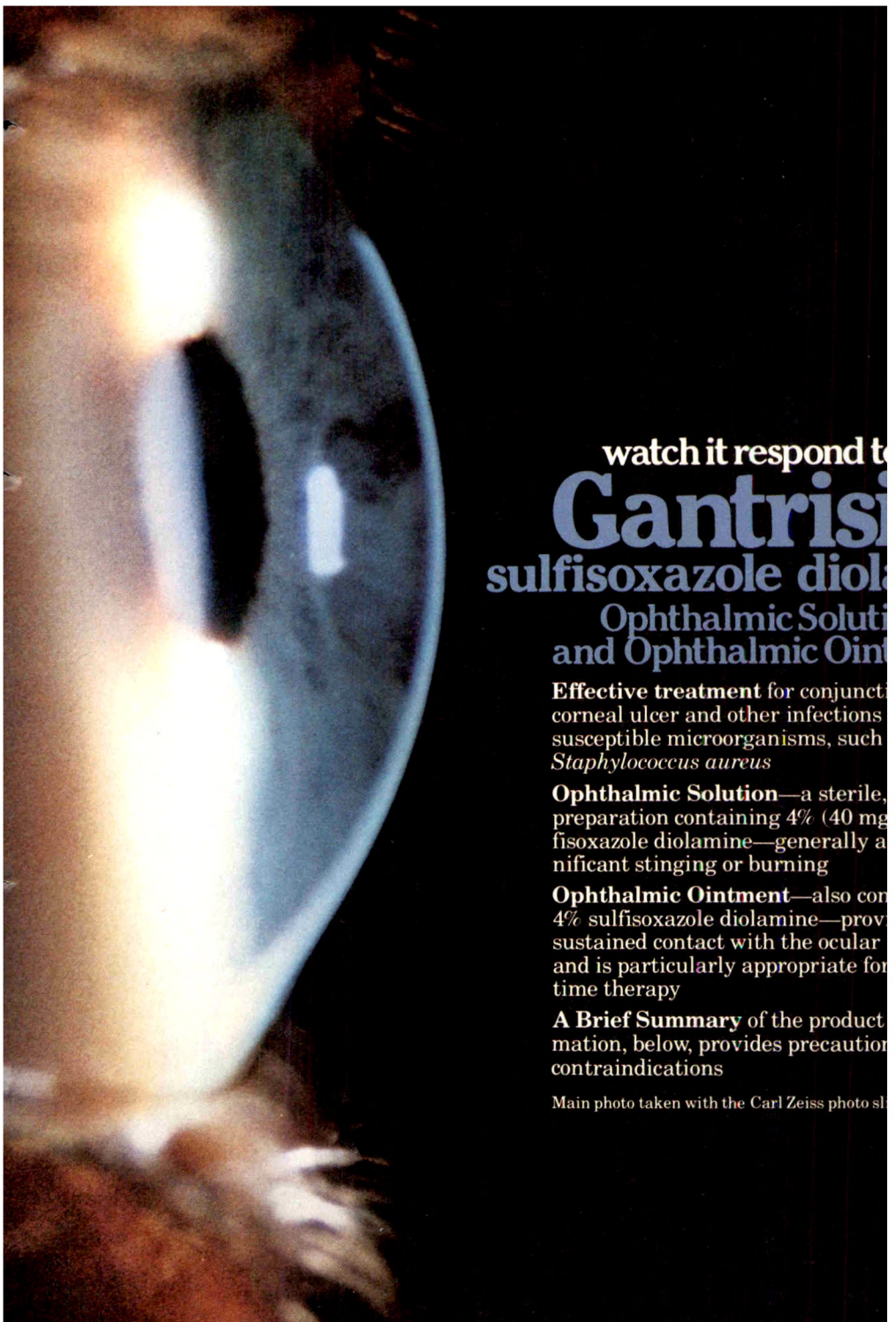

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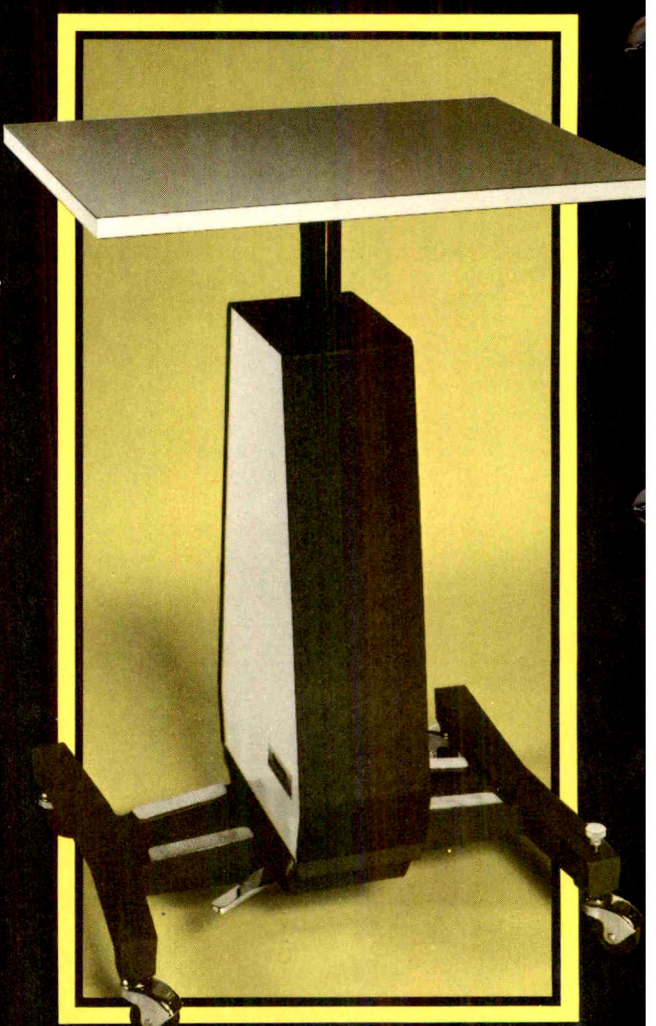

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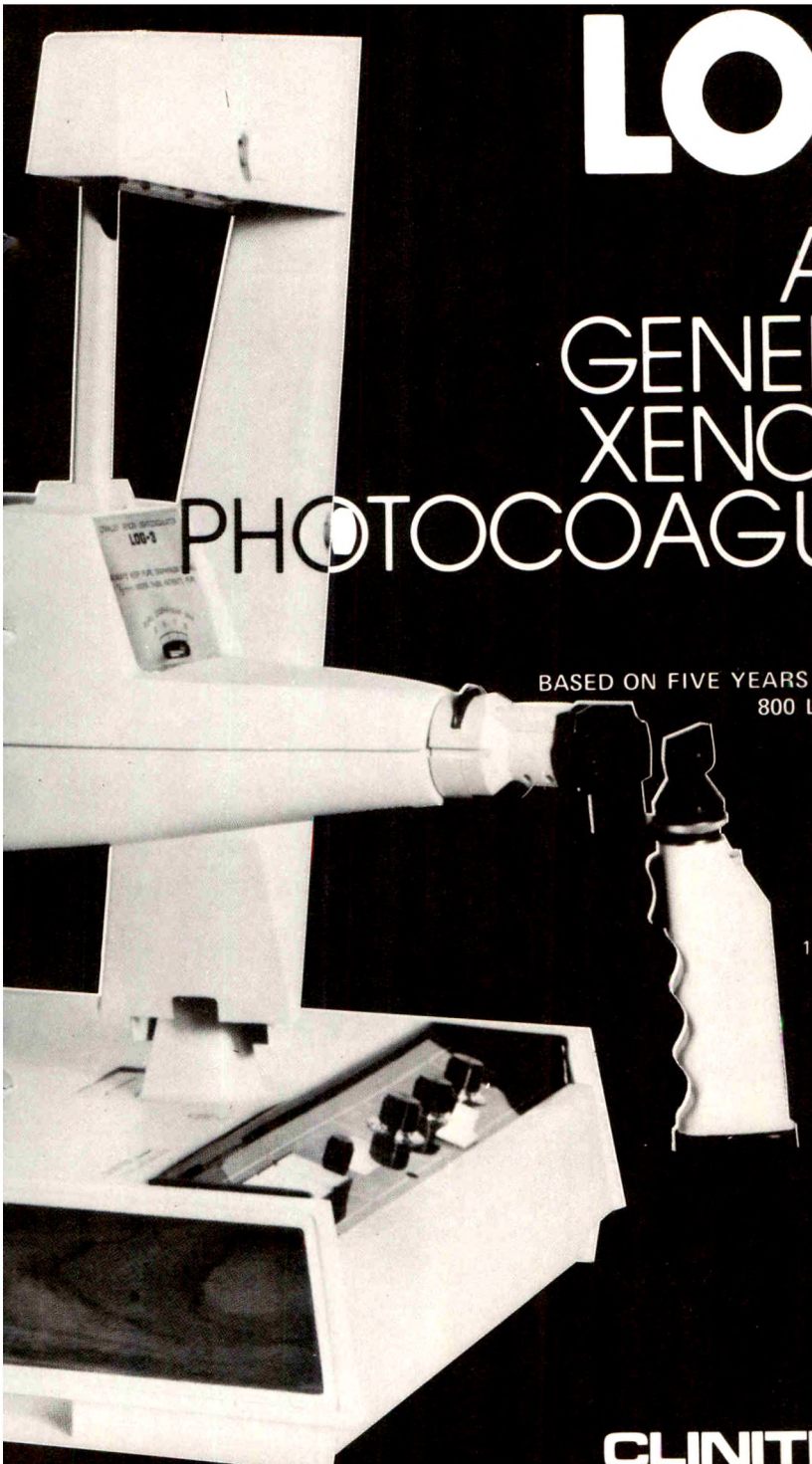

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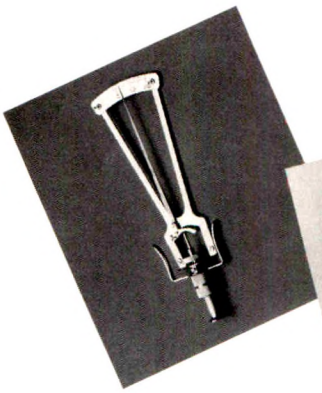

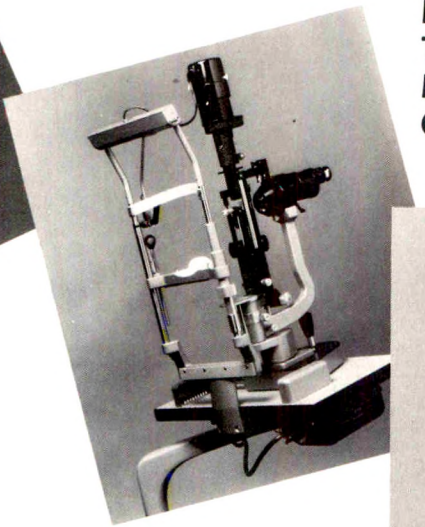

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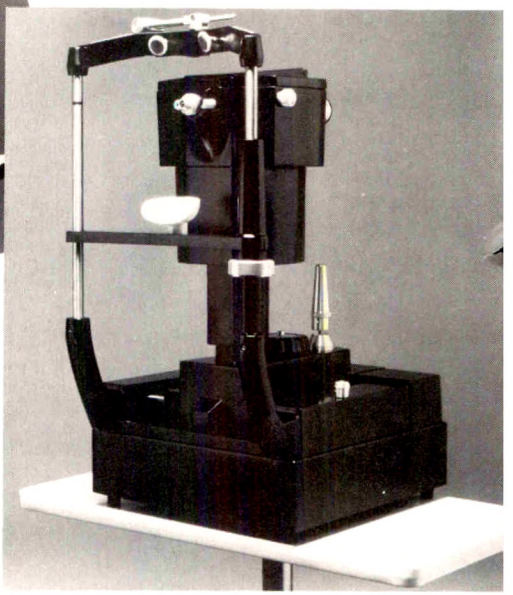

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References:
1. Obstbaum,S.A. et al. Timolol: Effect on intraocular pressure in chronic open-angle glaucoma. Ann Ophthalmol 10(10): 1347-1351, 1978
2. A study conducted by an independent research organization. Allergan Pharmaceuticals Report Series #148, 1979.

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INCREASED INCIDENCE OF CHOROIDAL MALIGNANT MELANOMA OCCURRING IN A SINGLE POPULATION OF CHEMICAL WORKERS

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Cincinnati, Ohio

A cluster of ocular cancers occurring among employees of the duPont Belle, West Virginia, plant in the Kanawha River Valley was brought to public attention by a laboratory worker at the plant who suspected that the overall occurrence of cancer among his fellow employees, particularly ocular cancer, was excessively high.[1] In 1976, a report by company epidemiologists on the occurrence of cancer at that plant indicated that a statistically significant excess number of cases of ocular cancer (all histologic types combined) and of kidney cancers had occurred among plant employees (M. O'Berg, unpublished data).

The National Institute for Occupational Safety and Health was asked to investigate the reported increased incidence at this plant. As part of this investigation, the Institute contracted with us to examine active workers at the plant and control workers from the surrounding area to determine the prevalence of ocular pigmented lesions in the workers as compared with the control group. This study was done with the cooperation of the duPont Belle plant management and medical staff.

We subsequently confirmed by histopathologic examination three cases of choroidal melanoma that occurred between 1972 and 1975 among active and former workers of the plant. Descriptions of two of these three cases have been published.[2] A fourth case, diagnosed in 1952, was subsequently identified by the duPont medical staff and confirmed by us. In a field study in 1978, we documented a fifth case of choroidal malignant melanoma in a retired worker from this plant. We have determined that this represents a statistically significantly greater than expected occurrence of choroidal melanomas in the plant white male population.

SUBJECTS AND METHODS

Histopathologic examination and documentation of cases of choroidal

From Harvard Medical School, Department of Ophthalmology, the Massachusetts Eye and Ear Infirmary and the Children's Hospital Medical Center, Boston, Massachusetts (Drs. Albert, Puliafito, Fulton, Zakov, Dryja, and Ms. Robinson); and the Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio (Drs. Smith and Leffingwell, and Ms. Egan).

Reprint requests to Daniel M. Albert, M.D., Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

melanoma—Two cases (Cases 1 and 2) were identified from a list of purported eye tumors occurring at the plant, which was given in testimony to the House Subcommittee on Oversight and Investigations in 1976.[1] Case 3 was reported to us by three physicians (W. Evins, B. H. Ginsberg, and S. W. Rosen, personal communication, 1977) in response to published correspondence.[2] Case 4 was identified by duPont physicians. Case 5 was diagnosed during the subsequent field study of active and retired workers at the plant. Representative histopathologic sections and medical histories were obtained from respective hospitals at which the patients were treated and the ocular studies were done. Information regarding work histories was made available by duPont.

Ophthalmologic survey of active and retired workers of the plant and comparison populations: Selection of study population—Evaluation of the work histories of the plant melanoma cases before undertaking the ophthalmologic survey showed no similarities in job assignment. Consequently, there was no a priori notion of the exposure or exposures to which the apparent risk of ocular melanoma might be attributed other than employment at the plant. The study population was, therefore, solicited from among active employees with the greatest amount of time elapsed since onset of employment. It was arbitrarily decided to limit participation to all employees with 15 years or greater of active service at the plant. Participation was also solicited from among retired plant employees living in West Virginia.

A group of nonindustrial worker volunteer examinees was solicited for a comparison population from among current employees of the West Virginia State Health Department, the West Virginia Civil Service Commission, the City of Charleston Office of Public Safety, the City of Charleston City Manager's Office, and from among members of the Chesapeake and Potomac Telephone Company's Pioneers of America, and the Charleston Lions Club. Preference for participation was given to men older than age 45 years, because a group roughly comparable to the plant employee population was desired and because the duPont population was predominantly male in the older age groups.

On-site ophthalmologic survey—Under contract with the National Institute for Occupational Safety and Health, the ophthalmologic survey of active and retired workers, described previously, was done in an attempt to identify additional cases of ocular neoplasms and to determine the prevalence of ocular pigmented lesions in this group as compared to the prevalence of these lesions in a group of individuals from the Kanawha River Valley (in which the plant is located) without current occupational exposure to the chemical industry.

Ophthalmologic examinations of duPont workers were conducted on site at the plant in space provided by the duPont Company. The comparison population was examined in space provided by the West Virginia State Department of Health. Informed consent was obtained before the examinations. Occupational, medical, and ocular histories were obtained from each participant examined. Participants were surveyed regarding history of cutaneous neoplasms; cutaneous moles that had changed, been removed, or newly developed; cutaneous lesions that had been excised or from which biopsy specimens had been taken; and history of other noncutaneous nonocular neoplasms.

The ophthalmologic examinations included determination of visual acuity, measurement of pupillary size, evaluation of pupillary reactivity, examination for exophthalmos, slit-lamp biomicros-

copy, applanation tonometry, dilated ophthalmoscopic examination, and when indicated, gonioscopy. All conjunctival, iris, and posterior choroidal nevi were photographed. Fundus drawings were made of those choroidal nevi located too peripherally to be photographed. Participants were informed verbally and again in subsequent letters of any abnormal findings, and local ophthalmologic consultation was advised.

Data regarding the incidence of choroidal melanomas in the state of West Virginia and Kanawha County—We reviewed records of all cases of ocular tumors reported to the West Virginia Central Cancer Registry for the period 1957 through 1976 and tabulated the number of cases of choroidal melanoma occurring in the individual counties of West Virginia. We reviewed, as well, death certificates filed with the West Virginia Bureau of Vital Records for all individuals within West Virginia whose death was attributed nosologically to cancer of the eye as the underlying cause of death for the years 1960 (the first year for which such records were computerized) through 1976.

Case reports

Case 1—A 57-year-old white man had worked at the chemical plant for 30 years (1942-1972). During that time, he had worked as an operator in various production areas, including the manufacture of alcohols, amines, ammonia, antifreeze, and nylon. Additionally, he had worked in a small lots production facility which, as the name implies, produced relatively small quantities of a wide variety of chemicals being tested for feasibility of commercial production.

In 1972 the patient had a ten-day history of poor vision in his left eye. Visual acuity was 6/6 (20/20) in the right eye and counting fingers at three feet in the left eye. Examination of the left ocular fundus showed a large intraocular tumor. Enucleation was performed, and subsequent histopathologic examination of the left eye revealed a malignant melanoma of the mixed-cell type (Fig. 1). The patient died of metastatic melanoma 18 months after enucleation.

Case 2—A 55-year-old white man worked at the

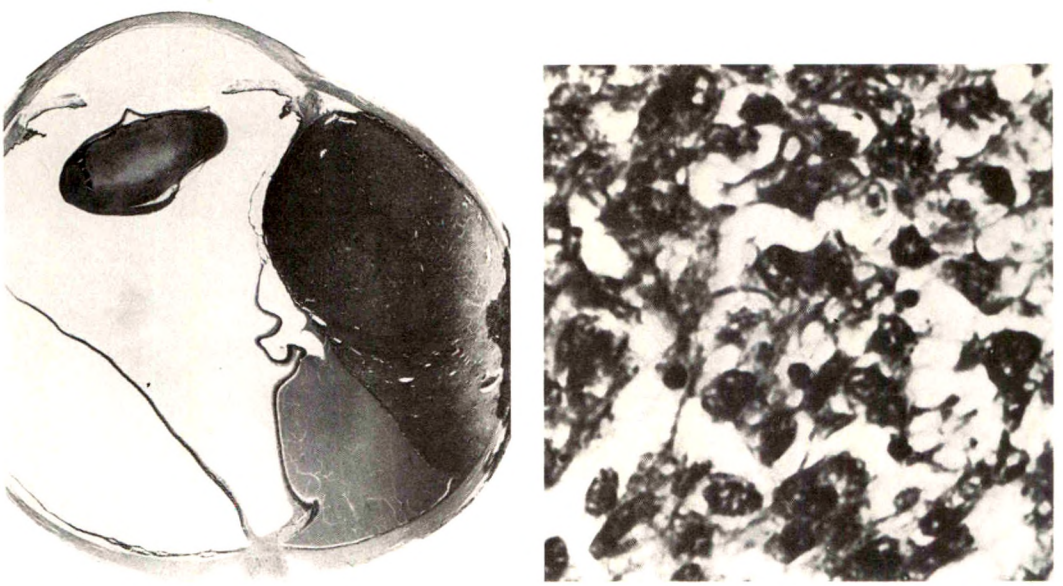

Fig. 1. (Albert and associates). Left, Low-power view showing melanoma extending from ciliary body to area posterior to the equator, with extensve retinal detachment and retinal degeneration overlying the tumor (hematoxylin and eosin, ×5.6). Right, Higher power view of tumor showing epithelioid and spindle B type cells, with numerous cells having extensive lipid deposits in cytoplasms, appearing as empty spaces after preparation (hematoxylin and eosin, ×560).

plant for 34 years (1941-1975). During that time, he had worked as an operator in various production areas, including hydrogenation and solvents, dimethylsulfate manufacture, small lots, and miscellaneous production.

In May 1974, the patient had complained of a "wavy sensation" in the central vision in his right eye. Examination of the right eye showed an intraocular mass, and evidence of growth was observed on follow-up examinations during the subsequent year. The right eye was enucleated in March 1975. Pathologic examination revealed a choroidal melanoma of the mixed-cell type (Fig. 2). The patient is alive and has shown no evidence of recurrence or metastases.

Case 3—A 38-year-old white man worked at the plant for approximately six months during his late teens in the early 1950s. He reported that he had worked in antifreeze production. Other pertinent occupational history included five years' work as a machinist at another chemical plant.

In April 1972, he had a history of progressive impairment of vision in his left eye for several years. Visual acuity was 6/6 (20/20) in his right eye; visual acuity in his left eye was hand motions. The right eye was unremarkable. Examination of the left eye showed neovascularization of the iris, anterior chamber inflammation, detachment of the sensory retina, and the presence of an orange-colored mass visible in the ocular fundus. A diagnosis of intraocular tumor was made and the eye was enucleated. Pathologic examination showed a spindle B melanoma (Fig. 3). The patient has been followed up subse-

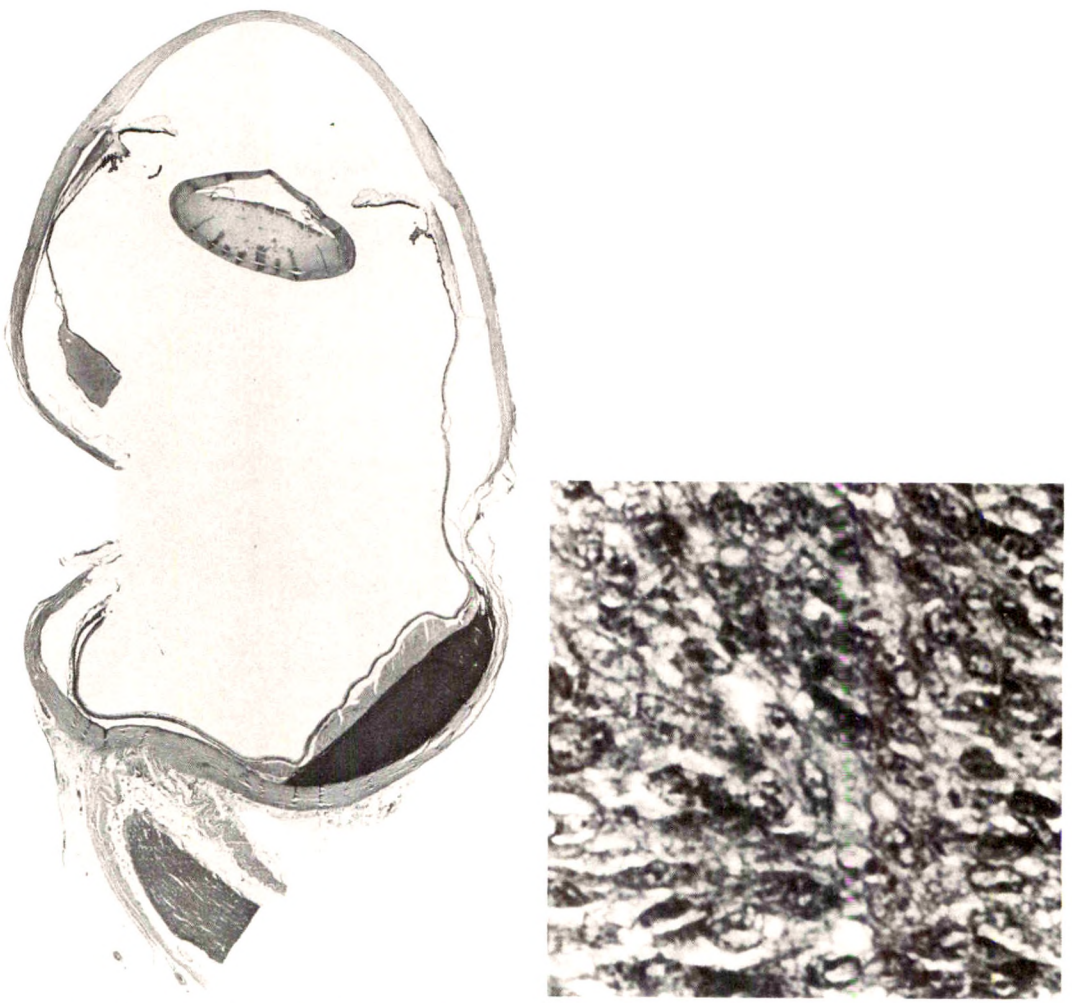

Fig. 2 (Albert and associates) Left, Low-power view of tumor in eye enucleated in Case 2. Relatively flat, densely pigmented tumor is seen. Perforation on opposite side of globe is artifactitious (hematoxylin and eosin, ×5.6). Right, Higher power view of epithelioid and spindle-shaped cells, composing the tumor (hematoxylin and eosin, ×560).

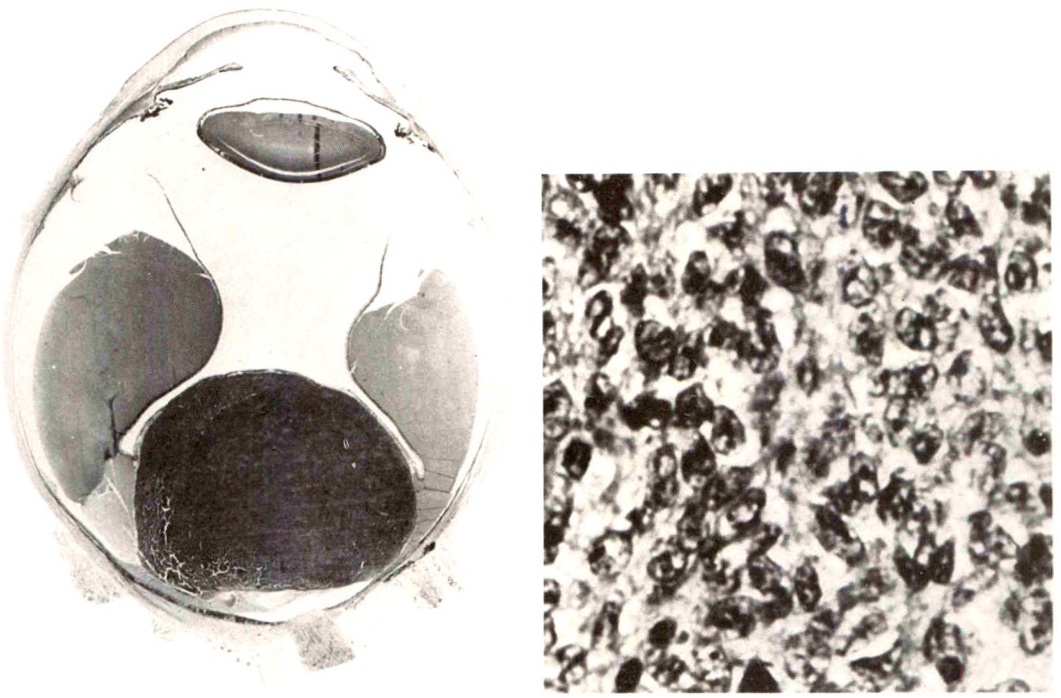

Fig. 3 (Albert and associates). Left, Low-power view of whole globe in Case 3 showing large posterior pole melanoma detaching retina with dense proteinaceous subretinal exudate (hematoxylin and eosin, ×5.6). Right, Higher power view of tumor seen in Case 3, showing clumped spindle B melanoma cells with moderately abundant cytoplasm, large nuclei, and numerous prominent nucleoli (hematoxylin and eosin, ×560).

quently without evidence of recurrence or metastatic disease.

Case 4—A 61-year-old white man worked at the plant for 20 years (1937-1957). His work assignments included work as a construction laborer, a janitor at the powerhouse, a general laborer throughout the plant, and a semiskilled laborer in the ammonia-alcohol plant.

In June 1972 the patient had a two-month history of visual disturbance in the right eye and a one-week history of visual field loss in the same eye. Visual acuity was R.E. 6/30 (20/100) and L.E. 6/18 (20/60). Ophthalmoscopic examination of the right eye revealed a large, gray, bullous detachment of the neural retina in the upper nasal quadrant, extending from the periphery to the disk. An area beneath the detachment that did not transilluminate light was noted. The eye was enucleated, and pathologic examination showed a choroidal melanoma of the mixed-cell type underlying the detached retina. The patient died of adenocarcinoma of the stomach.

Case 5—A 61-year-old white man worked at the plant for 41 years (1936-1977). During that time, he worked briefly as a laborer in ammonia and antifreeze production and as a tinsmith-sheetmetal worker throughout the plant for 37 years.

When examined during the on-site study in April 1978, the patient gave a history of decreasing visual acuity and pain in his left eye. Medical history was unremarkable except for several years' history of osteoarthritis. Ophthalmoscopic examination showed a lesion in the left posterior pole, which was believed to be a choroidal malignant melanoma. Subsequent to this examination, the patient sought further ophthalmologic consultation and the eye was enucleated. Histologic examination revealed a diffuse malignant melanoma of the choroid composed predominantly of epithelioid cells (Fig. 4) with secondary retinal detachment and papilledema.

Results

Results of the ophthalmologic survey at the plant—During the six weeks of the study, a total of 1,149 persons were examined. Of these, 591 were active plant employees (564 with 15 years or more of active service and 27 with less than 15 years of active service), 256 were retired plant employees, and 302 were nonindustrial worker participants. The percent participation by five-year groups among active plant employees eligible to

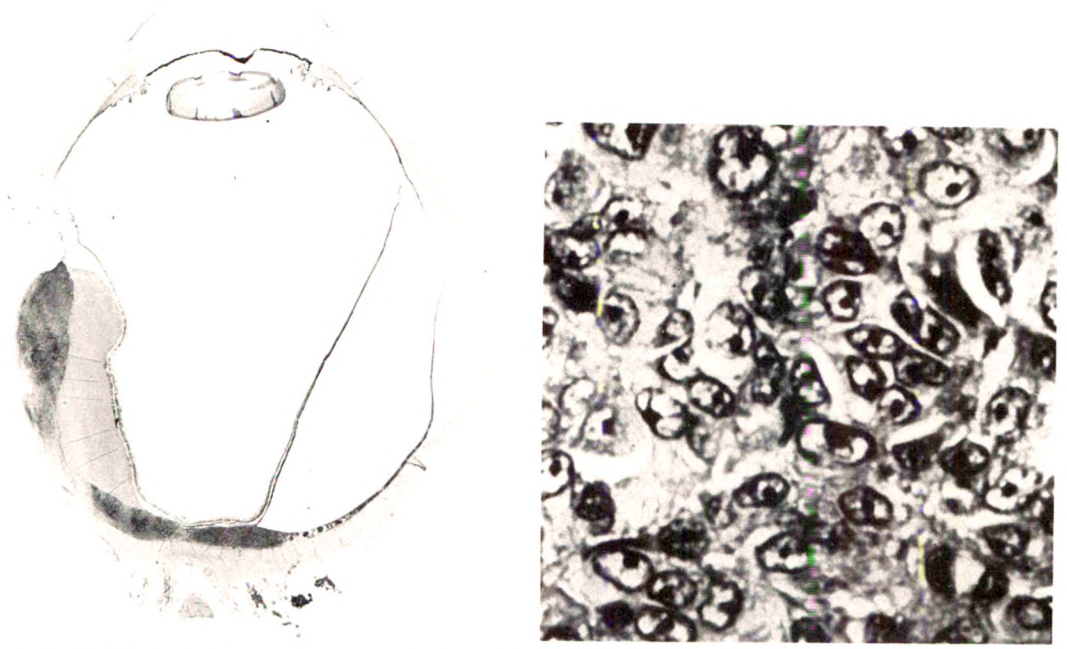

Fig. 4 (Albert and associates). Left, Relatively flat, infiltrative type of melanoma encircling optic nerve and resulting in extensive retinal detachment in enucleated eye from Case 5. Note extensive retinal detachment (hematoxylin and eosin, ×5.6). Right, Distinctly epithelioid pattern of cells comprising tumor (hematoxylin and eosin, ×560).

participate (sexes and races combined) is given in Table 1. Overall, 75.4% of active workers eligible to participate (that is, those with 15 or more years of active service) did so. Worker lists from which this determination was made did not identify individuals by sex or race, so that further breakdown of percentage participation by personal characteristics is not possible. However, based on our casual

TABLE 1

PERCENTAGE OF PARTICIPATION IN OPHTHALMOLOGICAL SURVEY AMONG DUPONT BELLE PLANT ACTIVE EMPLOYEES ELIGIBLE TO PARTICIPATE*, BY FIVE-YEAR AGE GROUP (SEXES AND RACES COMBINED)

Age Group (yrs)	No. of Employees* Eligible to Participate	Participation, %
<30	0	—
30-34	2	0
35-39	28	16.9
40-44	44	77.3
45-49	60	81.7
50-54	126	82.5
55-59	338	74.6
60-64	150	70.7
65+	0	—
Total	748	75.4

*Fifteen years or greater of active service. This eligibility criterion, chosen a priori, excluded from examination 970 employees with less than 15 years of active service.

observation, the worker population was almost exclusively white and, among hourly employees, male. Among the retired plant employees living in West Virginia, 256 out of 1,250 or 20.5%, participated. However, we do not have available the age, sex, or racial characteristics of the retired plant population to make a comparison of percent participation similar to that for active employees. Of the 847 (591 + 256) plant participants, 799 were white men, seven were nonwhite men, and 41 were white women. A breakdown by age of white male and female plant participants is given in Tables 2 and 3.

Among the 302 nonindustrial worker participants, 193 were white men, ten were nonwhite men, 93 were white women, and six were nonwhite women. Because the nonindustrial worker participants used for comparison were volunteers from diverse organizations, no assessment as to percentage participation relative to a target population can be made, as was done for active employees of the plant. The age breakdown for white male and female nonindustrial worker participants is given in Tables 2 and 3. The duPont white male participants tended to be older than the white male participants in the comparison group, whereas white female duPont participants and comparison participants tended to be similar in age.

The results of the ophthalmologic examinations are summarized in Table 4 for all participants; both sexes and races are combined. The most striking findings included the following:

1. A retired plant employee had a choroidal malignant melanoma (Case 5).

2. One iris melanoma was clinically diagnosed in a plant employee. The patient said the lesion had been present before employment at the plant, and it had been recognized clinically as an iris melanoma for some time. This employee had initially declined the examination and came to our attention through the efforts of the plant medical department, who persuaded him to undergo at least examination of the anterior segment of his eye. This case is not discussed further.

3. No choroidal melanomas were seen in the comparison population.

4. The overall prevalence of participants with conjunctival nevi (plant employees 0.9%; nonindustrial workers 0.7%) did not differ statistically significantly ($P > .1$) between participant groups. The overall prevalence of participants with iris nevi (plant employees

TABLE 2

SUMMARY BY AGE OF WHITE MALE PARTICIPANTS

Age (yrs)	duPont Participants		Comparison Participants	
	No.	Total duPont White Male Participants, %	No.	Total Comparison White Male Participants, %
20-29	0	0	3	1.6
30-39	37	4.6	22	11.4
40-49	80	10.0	47	24.4
50-59	338	42.3	69	35.8
60-69	305	38.2	41	21.2
70-79	36	4.5	9	4.7
80+	3	0.4	2	1.0
Total	799		193	

TABLE 3

SUMMARY BY AGE OF WHITE FEMALE PARTICIPANTS

Age (yrs)	duPont Participants		Comparison Participants	
	No.	Total duPont White Female Participants, %	No.	Total Comparison White Female Participants, %
20-29	0	0	2	2.2
30-39	3	7.3	2	2.2
40-49	8	19.5	12	12.9
50-59	22	53.7	60	64.5
60-69	8	19.5	12	12.9
70-79	0	0	4	4.3
80+	0	0	1	1.1
Total	41		93	

20.6%; nonindustrial workers 33.1%) and choroidal nevi (plant employees 6.9%; nonindustrial workers 10.9%) was statistically significantly greater in the nonindustrial worker group than in the plant group, with race and sex combined (continuity corrected chi-square: iris nevi, $P < .05$; choroidal nevi, $P < .05$). Analysis of white men and women on an age-stratified basis showed the overall prevalence of iris nevi still to be statistically significantly greater in the nonindustrial worker group than in the plant group, including both men and women. The prevalence of choroidal nevi among white men still was statistically significantly greater on an age-stratified basis, in nonindustrial workers than in plant employees. However, among white women, the prevalence of choroidal nevi was not statistically different between groups when analyzed on an age-stratified basis. Only one conjunctival nevus (in a nonindustrial worker) and one iris nevus (in a plant employee) were found among nonwhite participants. No choroidal nevi were identified among nonwhite participants. We do not believe these findings warrant statistical comparisons.

TABLE 4

SUMMARY OF EYE FINDINGS IN BELLE PLANT AND COMPARISON POPULATIONS

Finding	Belle Plant Population, %	Comparison Population, %
Fundus within normal limits	57.8	58.5
Choroidal melanoma	0.1	0
Iris melanoma	0.1	0
Choroidal nevi	6.9	10.9
Iris nevi	20.6	33.1
Conjunctival nevi	0.9	0.7
Eyelid lesions	3.0	6.6

Comparison of observed and expected number of choroidal malignant melanomas in active and retired plant employees (1952-1978)—To compare the observed with the expected occurrence of a disease such as cancer, in which there may be a long time lapse between its initiation and its detection, it is generally expedient to count the number of cases of the disease occurring during a specific period of time among members of a cohort of individuals who share some common antecedent factor, such as occupation. This observed number of disease occurrences is compared with the number expected to have occurred in that cohort over the same time period, were the cohort subject to the age-, sex-, race- and disease-specific rates of an appropriate referent popula-

tion. In the case of a rare disease, observed and expected numbers are generally compared by using a statistical test based on the Poisson distribution.

Although the number of choroidal melanomas expected to occur among active and retired plant employees from 1952 through 1978 was not directly determinable based upon data available to us, a reasonable estimate of the upper boundary of the expected number was calculated as follows: The cumulative age-stratified person years of observation for active and retired white male plant employees from January 1957 through June 1976 were obtained from an unpublished duPont Company study of cancer occurrence at the plant (M. O'Berg, unpublished data). These had been determined by company epidemiologists by summing the yearly plant census of active and retired white male plant employees, stratified by five-year groups. Person years of observation began in 1957 because yearly plant census data had not routinely been compiled before that year, and ended in 1976, because that was the date of the report. Two sets of referent rates were chosen to calculate the expected number of choroidal melanomas for comparison to the observed number. The first set consisted of white male age-specific incidence rates for melanomas of the eye, orbit, and lacrimal gland obtained from the National Cancer Institute's Third National Cancer Survey,[3] classified in accordance with the 1968 edition of the Manual of Tumor Nomenclature and Coding,[4] and included morphologic codes 8723, 8733, 8743, 8773, and 8783 (that is, malignant melanoma, amelanotic melanoma, malignant lentigo, spindle cell melanoma, and malignant blue nevus, respectively), and topographic codes 1900 through 1909 inclusively (that is, the globe, orbit, and lacrimal gland). The second set consisted of age-specific incidence rates for ocular melanoma obtained from the Connecticut State Tumor Registry (provided by John T. Flannery, Director, Connecticut Tumor Registry) by dividing the average (over the 20-year period 1957-1976) age-specific yearly occurrence of ocular melanomas among white male and female residents of Connecticut by the 1970 age-specific white (male and female) population distribution of the state of Connecticut. The ocular melanoma incidence rates of the state of West Virginia were not used as referent rates. Although a state central cancer registry had compiled statistics from 1957 onward, ocular tumors had been under-reported to the registry. For example, of 30 ocular melanoma deaths identified by reviewing all death certificates from 1960 through 1976 for individuals within West Virginia whose death was attributed nosologically to cancer of the eye, 17 of these 30 ocular melanoma deaths had not been reported to and were therefore unknown by the West Virginia Central Cancer Registry (A. B. Smith and E. Egan, unpublished data).

The expected number of ocular melanomas among plant white male employees from January 1957 through June 1976 was calculated by multiplying the cumulative age-stratified person years of observation by the appropriate age-specific referent incidence rates and summing over the age strata (Table 5). Because we do not have access to plant census data for the years 1952 through 1956 and 1976 through 1978, the overall expected occurrence of ocular melanoma from 1952 through 1978 was estimated by extrapolation from the period 1957 through 1976 to the period 1952 through 1978 by multiplying by 1.38, a weighting factor that represents the number of years from 1952 through 1978 divided by the number of years from January 1957 through June 1976. The resulting expected number of ocular melanomas among plant

TABLE 5

CALCULATION OF EXPECTED NUMBER OF OCULAR MELANOMAS AMONG DUPONT BELLE PLANT WHITE MALE EMPLOYEES*

Age Group (yrs)	Person Years of Observation, 1/57-6/76	Incidence of Ocular Melanoma per 100,000 (NCI Rates)	Expected Ocular Melanomas ($\times 10^{-5}$) (NCI Rates)	Incidence of Ocular Melanoma per 100,000 (Connecticut Rates)	Expected Ocular Melanomas ($\times 10^{-5}$) (Connecticut Rates)
15-19	95	0.04	3.8	0.02	1.9
20-24	1249	0.05	62.5	0.05	62.5
25-29	2189	0.15	328.4	0.05	109.5
30-34	2309	0.19	438.7	0.13	300.2
35-39	3229	0.20	645.8	0.22	710.4
40-44	6145	0.60	3687.0	0.28	1720.6
45-49	8869	0.60	5321.4	0.64	5676.2
50-54	10324	1.52	15692.5	1.04	10737.0
55-59	9956	1.85	18418.6	1.19	11847.6
60-64	7650	2.18	16677.0	1.81	13846.5
65-69	4207	2.43	10223.0	2.46	10349.2
70-74	2312	2.38	5502.6	2.38	5502.6
75-79	1060	2.65	2809.0	1.88	1192.8
80-84	285	2.14	609.9	1.94	552.9
85+	72	3.56	256.3	1.89	136.1
Total	59951		80676.5		62746.0

*NCI designates National Cancer Institute.

active and retired employees was then compared to an observed number of four cases (Cases 1, 2, and 4 among active employees, and Case 5 in a retired employee). Case 3 was not directly comparable because the duPont data base excluded person years of observation among short-term terminated employees.

Based on National Cancer Institute incidence rates, the expected number of ocular melanomas occurring among the plant's white male employees from January 1952 through December 1978 was 1.11 (expected number of ocular melanomas in plant employees equals expected number of ocular melanomas [National Cancer Institute rates] multiplied by the weighting factor, or, 1.11 = 80,676.5/100,000 [from Table 5] × 1.38 [as explained previously]). Based on Connecticut Tumor Registry incidence rates, the expected number of ocular melanomas occurring among plant employees was 0.87. A Poisson distribution was used to compare the expected numbers of ocular melanomas with the observed number of melanomas.[5] Given a Poisson distribution with a mean (or expected) value of 1.11 (National Cancer Institute referent rate), the cumulative probability of observing greater than three events (that is, four or greater events) is $1 - P(\text{observed} \leq 3) = 1 - 0.974 = 0.026$. Similarly, the probability of observing greater than three events (four or more events) using Connecticut Tumor Registry referent rates to derive an expected value of 0.87 (62,746.0/100,000 [from Table 5] multiplied by 1.38, as explained previously) is 0.013. Thus, the probability of observing four ocular melanomas among plant white male employees is less than 5% (that is, $P < .05$); the probability level that is generally chosen to represent statistical significance.

The expected and observed numbers of ocular melanomas, as outlined previously, were not determined from precise enumerations either of the cumulative person years of observation among plant employees or of the total number of cases that may be presumed to have occurred. Therefore, it is important to consider possible biases in the determination of both figures to see if the estimates of expected and observed are likely to be over- or underestimates of the true, but probably unknowable numbers.

THE OBSERVED—The primary surveillance system for identifying cancer cases among living individuals at the plant was based on data submitted to the company through claims filed on employees covered by the company-sponsored group health and accident program. This program covers active employees alone, and thus, a surveillance system based upon it would be unlikely to uncover cases occurring among terminated (such as Case 3) or retired (such as Case 5) employees. The finding of Cases 3 and 5 was thus serendipitous, the former because of alert physicians at the National Institutes of Health, and the latter because the individual volunteered to participate in our ophthalmologic survey. We have virtually no information on the 994 retired employees living in West Virginia who did not participate, not to mention the retired employees who may have died without mention anywhere, except for their private ophthalmologist's records, of possible eye problems. Therefore the observed of four (Cases 1, 2, 4, and 5; Case 3 is excluded as mentioned previously) is likely to be a conservative underestimate of the true occurrence.

THE EXPECTED—This was estimated by applying age-specific referent population rates to the cumulative person years of observation of the plant population. The National Cancer Institute's referent rates that were used included melanomas

(all cell types) of all structures of the globe, as well as the orbit (including connective tissue, fatty tissue, subcutaneous tissue, and extraocular muscles) and the lacrimal gland. Our studies have dealt solely with malignant melanomas of the choroid. Therefore, the National Cancer Institute rates are an overestimate of the rates most appropriate for direct comparison with our observations. Any expected number derived based on these rates must be an overestimate of the true number; hence, another conservative estimate. Additionally, were we to have referent rates for melanomas of the uveal tract alone, this would still be an overestimate of the appropriate rates, because between 7 and 21.5% of ocular malignant melanomas are nonchoroidal (that is, iris or ciliary body) in origin.[6-9] The necessity to extrapolate from the period of 1957 through June 1976 to the period of 1952 through 1978 introduces a possibility of error that is more difficult to estimate, but the result is still probably a conservative estimate. There were about 3,500 employees in 1952, including a larger number of older workers who were hired during World War II. The work force was reduced by attrition until 1973 when hiring to replace retired workers was resumed. Thus, for the period 1952 through 1957 the work force was older and larger than now, but the retired group was correspondingly smaller. Because incidence increases with age, and in this relatively static population of workers, the age of the population increased with time (that is, the average age was low in 1952 and high in 1976), the estimated incidence would tend to be enlarged during the base period of 1957 through 1976 so that extrapolation would overestimate the total number of cases for five years (1952-1956) and underestimate the expected for 2½ years (June 1976-1978).

Statistically, our estimates of expected and observed melanomas are both conservative and tend to inflate the true expected and to decrease the true observed melanomas. That our data remain statistically significant despite these biases, supports the hypothesis of greater than expected occurrence of this tumor among the plant employees. We have not gone through similar explanation for the Connecticut Tumor Registry-derived referent rates, because the expected number based on these rates was even less than the expected number based on National Cancer Institute rates.

West Virginia Central Cancer Registry data—Despite the evidence of underreporting of cases of ocular melanomas to the West Virginia Central Cancer Registry, we compiled available data to determine if the reporting rate was greater than or less than the referent rates cited previously, and to compare reporting within Kanawha County to the state as a whole.

The average annual reporting rate of ocular melanoma in West Virginia from 1957 through 1976 was 0.25/100,000 based on 1970 population figures. An analysis of cases by county revealed the greatest number of reported cases that occurred in Cabell County (in which the city of Huntington is located). The annual reporting rates for Cabell County, Kanawha County, and West Virginia exclusive of Cabell and Kanawha Counties were 0.795/100,000; 0.28/100,000, and 0.234/100,000, respectively. Thus, the reporting rate for Kanawha County did not largely differ from that of West Virginia as a whole and was less than the incidence rates used by us in determining the expected number of ocular melanomas at the plant.

Exposure of plant employees to chemicals with known or suspected carcinogenic potential—On the basis of information made available by duPont, it was learned that the chemical manufacturing

facility at which these men worked used a variety of organic chemicals with known or suspected carcinogenic potential. A review of the list of raw materials and products showed 13 substances to be on the list of suspected carcinogens compiled by the National Institute for Occupational Safety and Health. A variety of secondary amine compounds were present that are believed possibly to form nitrosamine compounds either in air or in water. Of the substances listed, 65% were not covered by Occupational Safety and Health Administration standards, including two suspected carcinogens.

With regard to specific exposures of employees in Cases 1 to 5, exposure histories are incomplete, and information on exposure or possible exposure to multiple agents is incomplete. Consequently, we believe it inappropriate to attempt to discuss specific chemical exposures at this time.

Discussion

As a result of our investigations, we documented a total of five cases of choroidal malignant melanoma occurring among present or former workers of the duPont Belle, West Virginia, plant from 1952 through 1978. In all of the cases the involved eye was enucleated, and histopathologic confirmation of the diagnosis was made. Based on estimation of expected melanomas the occurrence was statistically significantly greater than expected.

In terms of the self-reported medical histories obtained during our field study at the plant, a greater self-reported history of cancer (all sites combined) among those participants was recorded that was significantly greater than the comparison group ($.01 < P < .025$) on an age-stratified basis. Also, from the self-reported medical history of certain skin conditions (moles that have appeared, changed, or been surgically removed; and skin surgery), both groups were comparable. This indicates that there was apparently not a higher rate of cutaneous melanoma in the plant employees.

These five cases of choroidal melanoma occurring in active and pensioned plant employees appear to us to be striking, particularly because three of these cases (Cases 1, 2, and 3) were diagnosed in a 25-month period (April 1972 through May 1974) and four cases (excluding Case 4, which was diagnosed in 1952) occurred within a 72-month period. These findings indicate that there may be a large increase over the expected number for the overall period of observation, particularly because choroidal melanoma occurs rarely. Choroidal melanomas have an age-adjusted (to the 1970 United States population) annual incidence in the United States of 6/100,000 population among whites and 0.7/100,000 population among blacks.[10-12] Worldwide, the annual age-adjusted (to the world standard population as described by Doll and associates[13]) incidence is reported to range from 2/100,000 among certain Asian countries to 10/100,000 among the Scandinavian countries.[14] Such disparities may be related to differences in ascertainment and reporting presumed to exist between countries, with relatively more complete reporting occurring among the Scandinavian countries. Malignant melanomas of the choroid and ciliary body, however, constitute the most common primary intraocular tumor in adults.

To the best of our knowledge, the present study represents the first reported association between an occupation and an increased risk for ocular melanomas. The cause of these neoplasms is not known. As noted previously, the possibility of exposure to multiple agents and

incomplete exposure histories, one or more specific carcinogens, or common job assignments cannot be implicated. However, melanomas have been induced in laboratory animals by chemical agents. One of us (D.M.A.) has induced melanomas in rats by the intravitreal injection of nickel subsulfide (unpublished data). Benson[15] reported intraocular tumor development in rats after orally administered ethionine and N-2-fluorenylacetamide. Patz, Wulff, and Rogers[16] produced fibrosarcomas of the choroid in rats by intraocular introduction of methylcholanthrene. In dogs, ocular melanomas have been produced by radium.[17]

The pathogenesis of ocular melanomas is not well understood. It has long been believed that pre-existing choroidal nevi may undergo malignant change into melanomas, although the evidence for this hypothesis is largely presumptive.[18–20] In the on-site study, however, the overall percentage of participants with iris nevi and choroidal nevi was significantly higher in the nonindustrial workers (comparison group) than in the plant workers. The significance of this finding is not clear.

One important aspect that should be noted with regard to Case 3 is that the patient was only 38 years old at the time of diagnosis of his tumor. On the basis of the history of progressive loss of vision over several years, this tumor was probably present for many years before diagnosis. Choroidal melanoma is frequently a neoplasm of the seventh or eighth decade. The average age at diagnosis is 56 years.[8] It occurs rarely in the younger age groups; the approximate annual incidence in the 35- to 44-year age group is 0.2/100,000 population.[3] It has long been stressed that when cases of rarely occurring tumors are documented among relatively young persons, an occupational or environmental exposure should at least be considered.[21] Moreover, the relatively short length in Case 3 of employment does not exclude an environmental cause, because several studies have indicated that relatively short exposures (for example, six months to one year) may appreciably increase the risk of cancer.[22] In a study of occupation and cancer of the lower urinary tract, it was concluded that the duration of occupational exposure adequate to increase the risk for cancer was less than two years.[23]

Summary

In five patients with choroidal melanoma occurring among present or former workers of the duPont Belle, West Virginia, plant the involved eye was enucleated and histopathologic confirmation of the diagnosis was made. This represents a statistically significantly greater than expected occurrence of choroidal melanomas in the white male study population.

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FILTERING VALVE IMPLANT SURGERY FOR EYES WITH NEOVASCULAR GLAUCOMA

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Neovascular (hemorrhagic) glaucoma responds poorly to both medical and surgical management, and is considered to be one of the most difficult forms of glaucoma to control.[1] In neovascular glaucoma fibrovascular tissue grows over the surface of the iris and trabecular meshwork. This growth results in marked impairment of outflow facility and increased intraocular pressure (IOP). Standard filtering surgery in neovascular glaucoma is particularly unsuccessful because of proliferation of fibrovascular tissue, closure of the sclerostomy site, and scarring of the filtering bleb.

A unidirectional and pressure-sensitive glaucoma valve implant described in 1976[2] has been modified for use in eyes with neovascular glaucoma. We describe our experience with the valve implant in 42 eyes with neovascular glaucoma.

MATERIAL AND METHODS

Valve implant—The glaucoma valve implant (Fig. 1) consisted of the following three major components:

1. An open Supramid tube with an outside diameter of 0.58 mm and an inside diameter of 0.38 mm. This tube was approximately 10 mm in length and was cut

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Fig. 1 (Krupin and associates). Glaucoma valve implant consists of (1) an open Supramid tube that is placed into the anterior chamber; (2) a Silastic tube that contains a pressure-sensitive and unidirectional valve (arrow); and (3) Supramid sidearms.

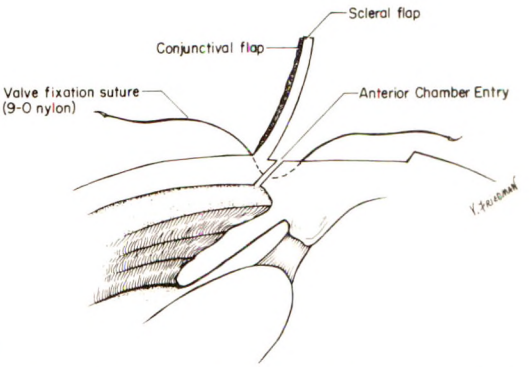

Fig. 2 (Krupin and associates). Entry wound for the glaucoma valve is made in clear cornea, parallel to the plane of the iris. A mattress fixation suture is passed across the entry wound.

at the time of surgery to extend 1 to 4 mm into the anterior chamber.

2. A Silastic tube that was attached at a 160-degree angle to the Supramid tube: The end of the Silastic tube was sealed and contained horizontal and vertical slits that functioned as a pressure-sensitive and unidirectional valve. Manometric testing indicated an opening pressure between 11 and 14 mm Hg with a closing pressure of 1 to 2 mm Hg lower. The Silastic portion extended 2 to 3 mm posterior to the corneoscleral limbus and was covered with a partial thickness scleral flap during surgery.

3. Two horizontal Supramid sidearms were cemented to the implant. The sidearms were sutured to the sclera at the anterior chamber entry site to prevent posterior migration of the implant.

Surgical procedure—Surgery was performed under local anesthesia (retrobulbar and eyelid blocks) using an operating microscope. An eyelid speculum was inserted and a superior rectus muscle bridle suture was placed. A conjunctival flap was prepared 6 to 8 mm from and parallel to the corneoscleral limbus superiorly. The flap was turned down over the cornea to expose the surgical corneoscleral limbus. Cautery was applied to episcleral vessels. A 5- to 6-mm square limbal based scleral flap, one half to two thirds of the scleral thickness was made. The scleral lamellar flap was dissected into clear cornea (Fig. 2). Entry into the anterior chamber was made in clear cornea either with a No. 55 Beaver keratome or a razor blade knife. This incision was parallel to the plane of the iris and 2.5 mm in length. An iridectomy was performed only if the iris entered the wound.

A double-armed 9-0 nylon or polypropylene suture was used for valve fixation. In most cases this was passed across the entry wound from the corneal side to the scleral side in a mattress fashion (Fig. 2). An alternative method was to place the mattress suture across the wound from within the lamellar bed. In either method the two ends of the suture exited on the scleral side 1 mm posterior to the entry incision (Figs. 2 and 3A).

The Supramid end of the autoclave sterilized valve implant was attached to a No. 27 hypodermic needle and was irrigated with balanced salt solution. The Silastic valve end of the implant was manipulated with smooth forceps to assure proper setting of the valve flaps. The implant was removed from the hypodermic needle and placed on a sterilized wood blade. The Supramid tube was fixated and cut to a length of 2 to 4 mm (from the sidearms) with a surgical blade. The exact length was dependent upon the status of the particular eye and selected to

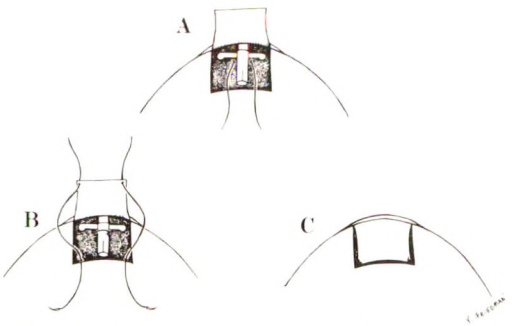

Fig. 3 (Krupin and associates). (A) Glaucoma valve implant in place with the two sides of the fixation suture behind the sidearms. (B) The fixation suture is tied posterior to the sidearms and over the top of the implant. The interrupted sutures for closure of the scleral flap are recessed approximately 0.5 mm inward from the corners of the scleral bed. (C) Scleral flap closure.

allow the open end of the Supramid tube to extend 1 to 4 mm into the anterior chamber (Fig. 4). The open end rested in the anterior chamber without contacting the iris or cornea. The mattress suture was passed under and tied posterior to the sidearms, over the top of the implant (Fig. 3A and B). This suture stabilized the device, prevented posterior migration, and closed the incision. The scleral flap was closed over the Silastic tube with two interrupted 9-0 nylon or polypropylene sutures. The two corners of the scleral flap were recessed approximately 0.5 mm inward from the corners of the scleral bed

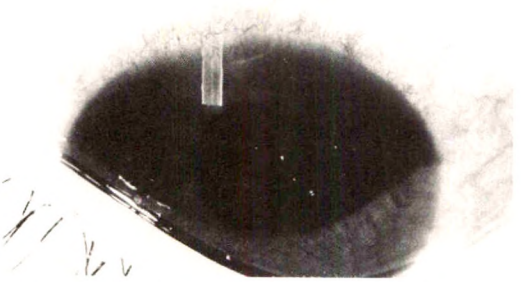

Fig. 4 (Krupin and associates). Supramid part of implant extends 1 to 4 mm into the anterior chamber without contacting the iris or cornea.

in order to prevent pressure of the scleral flap on the implant (Fig. 3B and C). The conjunctiva was closed with a running suture.

Postoperative therapy included atropine 1% administered topically twice daily and dexamethasone 0.1% or prednisolone 1.0% acetate administered topically four to six times daily for six to ten weeks. Corticosteroids were administered topically as needed for the marked postoperative inflammatory response seen in eyes with neovascular glaucoma. Ocular massage was initiated whenever the IOP increased to over 15 mm Hg.

RESULTS

We performed the filtering valve implant procedure in 42 eyes with neovascular glaucoma. In all eyes neovascularization was actively involving the entire iridocorneal angle with 360 degrees of synechiae or fibrovascular closure. The implant could not be used in two eyes because of diffuse bleeding from the scleral dissection and iridectomy. The mean age of the remaining 40 patients was 49.0 ± 15.2 (± S.D.) years (range, 19 to 68 years). Eight patients were black and 32 were white. Twenty-two patients were male. Rubeosis iridis was associated with diabetes mellitus in 22 eyes, central retinal vein occlusion in 12 eyes, chronic ocular inflammation in three eyes (one eye with Fuchs' heterochromic iridocyclitis), retrolental fibroplasia in two eyes, and Leber's miliary aneurysms in one eye. Preoperative IOP ranged between 36 and 72 mm Hg (mean, 52.7 ± 11.4 mm Hg) while combinations of topically administered epinephrine and pilocarpine, and orally administered acetazolamide were used. Most patients were also treated with topically administered corticosteroids before surgery.

Intraocular pressure could be maintained at ≤ 24 mm Hg postoperatively in 27 of the 40 eyes (68%) with a mean

TABLE 1

FAILURES WITH FILTERING VALVE IMPLANT

Complication	No. of Eyes
External bleb scarring	11
Posterior valve migration	1
Flat anterior chamber	1

follow-up of 13.8 ± 3.9 months (range, eight to 21 months). Seventeen of these 40 eyes (43%) required no medication and had a mean IOP of 17.0 ± 4.8 mm Hg (range, 8 to 24 mm Hg, 14.1 ± 3.8 months' duration). In ten eyes medical therapy was required (topically administered epinephrine and timolol, and orally administered acetazolamide), which resulted in a mean postoperative IOP of 17.7 ± 4.1 mm Hg (range, 10 to 24 mm Hg, 13.5 ± 4.4 months' duration).

The glaucoma valve implant failed to keep IOP below 24 mm Hg in the remaining 13 of the 40 eyes (32%) (Table 1). Failure resulted from external bleb scarring in 11 eyes. In five of these eyes there was melting of the scleral flap with visualization of the Silastic valve portion of the implant beneath the conjunctiva. However, two eyes with a functioning procedure also had scleral flap melting. Surgery was unsuccessful in one of the two eyes with retrolental fibroplasia because of a flat anterior chamber and in the other because of external scarring. Failure occurred in one eye with persistent ocular inflammation secondary to a dislocated lens nucleus in the vitreous.

Complications associated with the filtering valve implant are presented in Table 2. Fibrovascular growth was visible around the base of the anterior chamber Supramid tube. In two eyes tissue growth advanced to occlude the anterior chamber opening of the tube. Argon laser treatment effectively eliminated this tissue in both cases. One of these eyes was subsequently controlled, but in the other eye the valve migrated posteriorly and had to be removed. Postoperative hyphema that cleared spontaneously occurred in eight eyes. One eye developed a postoperative ciliochoroidal detachment that was drained. External erosion of the valve portion of the device through the conjunctiva occurred in one eye. This patient had Fuchs' heterochromic iridocyclitis. The IOP was controlled and the eye has remained free of inflammation.

DISCUSSION

The results of medical treatment of eyes with rubeosis iridis and neovascular glaucoma is often unsatisfactory. Topically administered corticosteroids and cycloplegics may relieve ocular discomfort, but do not control the glaucoma.[3] Topically administered miotic therapy generally does not lower IOP and may cause increased ocular inflammation and pain. Intraocular pressure may be decreased

TABLE 2

COMPLICATIONS ASSOCIATED WITH FILTERING VALVE IMPLANT

Complication	Procedures	
	Functioning (No.)	Failed (No.)
Scleral flap melting	5	2
Tissue growth around implant	1	1
Hyphema	6	2
Ciliochoroidal detachment	1	—
External erosion through conjunctiva	1	—

in some eyes with systemic carbonic anhydrase inhibitors, and topically administered epinephrine and timolol. However, medical glaucoma therapy ultimately fails in most cases because of progressive closure of the angle with fibrovascular tissue.

Rubeosis iridis may result from chronic ocular ischemia.[4,5] Retinal photocoagulation by eliminating ischemic retinal tissue may cause a regression of iris neovascularization.[6–9] In some eyes before there is heavy fibrovascular involvement of the angle or formation of peripheral anterior synechiae, panretinal photocoagulation may also reduce IOP. However, recurrence of iris and angle neovascularization often occurs. Direct argon laser treatment (goniophotocoagulation) of angle neovascularization also may be effective before the angle is closed by synechiae.[10] Once neovascular glaucoma with angle closure is established, both panretinal photocoagulation and goniophotocoagulation are usually ineffective. Regression of iris neovascularization in diabetic angiopathy has been reported after adrenalectomy,[11] hypophysectomy,[12] and pituitary stalk section.[13] These radical methods have many undesirable side effects and are rarely used.

Cyclocryotherapy is sometimes useful in lowering IOP and relieving pain in neovascular glaucoma.[14,15] However, the procedure does nothing to open the occluded angle and improvement is often only temporary. Cyclocryotherapy may be associated with a high incidence of complications including cataract formation, anterior segment necrosis, blindness, and phthisis bulbi.[16,17] In a recent series of neovascular glaucoma subjected to a cyclocryotherapy, 24 of 41 eyes (58.5%) lost light perception.[18] Although cyclocryotherapy may relieve the pain of neovascular glaucoma, the high incidence of serious complications limits its usefulness in eyes with visual potential. In blind, painful eyes ocular comfort can also be achieved by retrobulbar alcohol injection[19] or enucleation.

The results of routine filtration surgery are disappointing in eyes with neovascular glaucoma.[1] Either prolonged postoperative inflammation or continued growth of fibrovascular tissue often closes the filtering site. A modified trabeculectomy using bipolar cauterization to the iris, sclerostomy site, and ciliary processes may provide improved surgical results (J. Herschler, M.D., unpublished data, 1979).

Molteno, Van Rooyen, and Bartholomew[20] describe the use of an implant in 12 eyes with neovascular glaucoma. This device consists of a silicone rubber tube that is placed into the anterior chamber. The tube extends 16 mm posterior to the corneoscleral limbus where it is attached to a thin circular acrylic episcleral plate. The plate is 13 mm in diameter and attached to the sclera. They reported success (pain-free and IOP less than 30 mm Hg) in all 12 eyes.

In the present series the filtering valve implant procedure was successful in 27 (68%) of 40 eyes with advanced neovascular glaucoma, that is, eyes having 360 degrees of angle closure by synechiae or fibrovascular tissue. This is encouraging considering the poor success and complications associated with other available modes of therapy. In the original design of the valve implant the anterior chamber Supramid tube rests in the iridocorneal angle.[2] The present modified implant operation places the Supramid portion of the valve implant into the anterior chamber. Thus, the effective opening of the sclerostomy is placed away from the iridocorneal angle. Although growth of fibrovascular tissue occurs around the base of the implant in the angle, this rarely extends to the open end (only two eyes in the present series). The long Supramid tube appears to reduce the occurrence of

sclerostomy closure and surgical failure. However, the valve implant does not eliminate external scarring of the bleb. This is still a major postoperative problem and requires corticosteroid therapy and the use of ocular massage. The valve implant is an alternative surgical procedure for achieving IOP control in eyes with neovascular glaucoma and visual potential. A randomized clinical study comparing the valve implant and the modified bipolar cautery trabeculectomy is presently being conducted.

Summary

We performed filtration surgery with a unidirectional, pressure-sensitive valve implant in 40 eyes with neovascular glaucoma. The device consisted of an open Supramid tube (outside diameter 0.58 mm, inside diameter 0.38 mm) sealed to a Silastic tube with a slit valve. The Supramid tube was inserted at the corneoscleral limbus 1 to 4 mm into the anterior chamber and the Silastic portion was located under a lamellar scleral flap. Twenty-seven of 40 eyes (68%) had a postoperative IOP ≤ 24 mm Hg with a mean follow-up of 13.8 months. Ten of these 27 eyes required postoperative medical therapy to achieve this level of IOP control. The glaucoma valve implant failed to return IOP to normal in 13 of the 40 eyes (32%), 11 of these as a consequence of scarring of the external bleb.

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LIMBAL PNEUMATONOMETRY

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Tonometry on deformed or edematous corneas is inaccurate with commonly used methods including Schiøtz and Goldmann applanation. In such diseased eyes, accurate pressure measurements may be especially critical for effective management. However, distortion from scarring or edema may leave the juxtalimbal area and corneoscleral limbus relatively normal. Even if only a single quadrant remains relatively disease-free, limbal or paralimbal corneal tonometry will have clinical value, provided the method is sufficiently accurate. Additionally, application of an instrument to an epithelial surface weakened by disease is avoided.

This study was designed to test the reliability of measurements made at the corneoscleral limbus of normal corneas with the Langham pneumatonograph[1,2] relative to conventional Goldmann tonometry at various pressures.

MATERIAL AND METHODS

Intraocular pressures in Bellevue Hospital Eye Clinic patients were tested on the same visit by Goldmann applanation and by the pneumatonograph applied to the central cornea and the limbal area with the patient in both sitting and supine positions. Topical proparacaine anesthesia was used throughout the testing period. Limbal pneumatonograph measurements were made with the 5-mm diameter sensor tip bisected by the apparent corneoscleral limbus. In older eyes, the anatomic transition at the corneoscleral limbus was sometimes obscured by senility changes, so that some variation in positioning was inevitable. In such cases, the most apical edge of the sensor tip rested on clear cornea. Placement variation was estimated to be no more than 1.5 mm from one eye to the other.

In order to expand the range of pressures, both glaucomatous and nonglaucomatous eyes were measured. Of 131 eyes examined, 58 (44%) were known to have glaucoma in various phases of treatment, but none had corneal disease, edema, or previous surgery. The patients ranged in age from 15 to 84 years, the average age was 50 ± 18 (S.D.) years, and 37 (55%) were female. The order of measurement was as follows: Goldmann applanation; pneumatonograph, sitting-center; pneumatonograph, sitting-limbal. The patient then assumed a supine position. After a minimum of two minutes, pneumatonograph supine-center was followed by pneumatonograph supine-limbal. All

TABLE 1

MEANS AND STANDARD DEVIATIONS FOR VARIOUS MODES OF IOP MEASUREMENTS

Mode	Mean Measurement (mm Hg)	S.D. (mm Hg)
Goldmann applanation	17.1	4.7
Pneumatonograph		
Sitting-center	18.4	4.5
Sitting-limbal	19.2	4.9
Supine-center	20.0	4.4
Supine-limbal	20.1	4.8

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TABLE 2

TWO-TAILED, PAIRED SAMPLE *t*-TEST FOR DIFFERENCES IN MEANS*

Comparison Between Modes of IOP Measurement	Mean Difference (mm Hg)	S. D. (mm Hg)	P Value
Goldmann minus PTG, sitting, center	−1.3	1.8	<.001
Goldmann minus PTG, sitting, limbal	−2.1	2.6	<.001
Goldmann minus PTG, supine, center	−2.9	2.2	<.001
Goldmann minus PTG, supine, limbal	−3.0	2.8	<.001
PTG, sitting (center minus limbal)	−0.8	2.5	<.001
PTG, supine (center minus limbal)	−0.1	2.9	>.50

*PTG designates pneumatonograph.

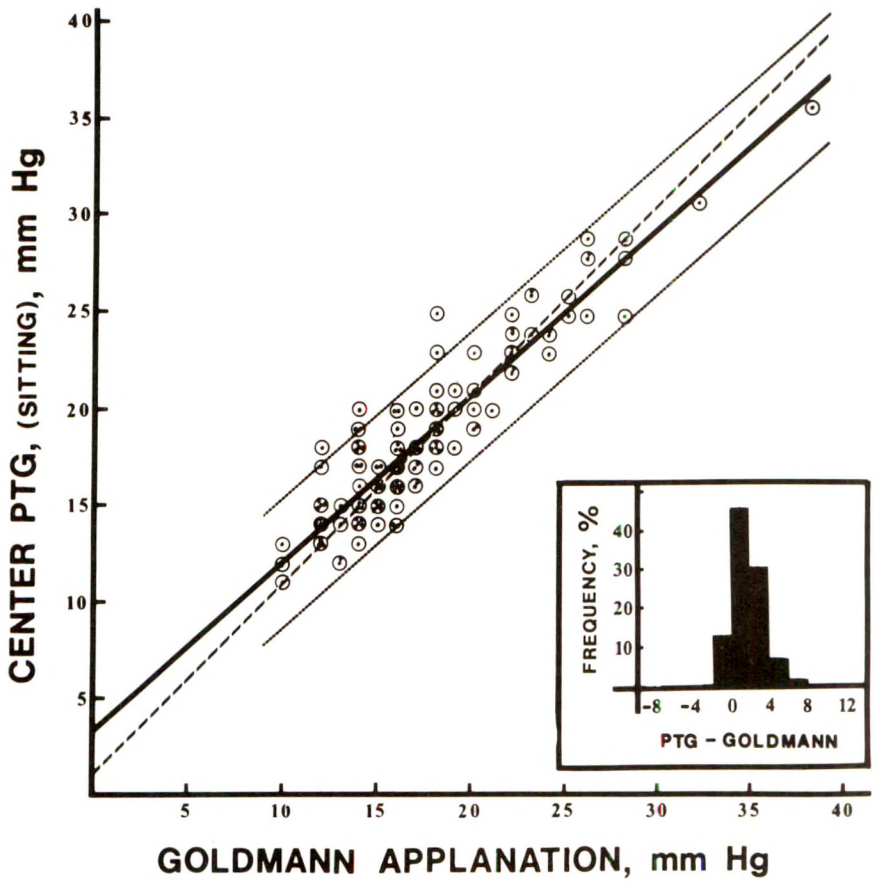

Fig. 1 (Breitfeller and Krohn). Relationship between applanation and pneumatonometric (center, sitting) IOP measurements. Plot of paired measurements on the same eye: the number of dots within a circle indicates the number of values with the same coordinates; the solid straight line is the regression; the dotted lines are the 95% confidence limits for the prediction of Goldmann from pneumatonograph (PTG) (inverse prediction); the dashed line has a slope of 1 and a unit *Y*-intercept, representing values predicted by use of the Clinical Correlation Estimator for the relationship depicted. Histogram: the frequency distribution of the difference between the pneumatonograph and the applanation values in the same eye. Note the correspondence between the value of maximum frequency and the Clinical Correlation Estimator (*Y*-intercept of the dashed line).

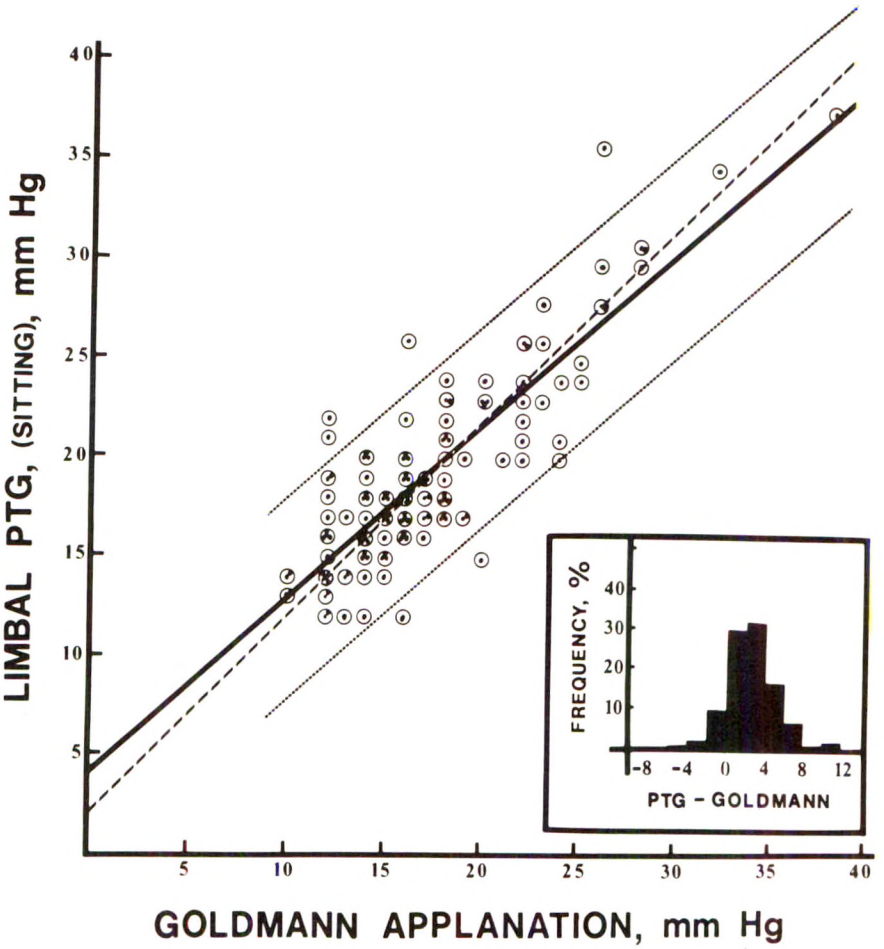

Fig. 2 (Breitfeller and Krohn). Relationship between applanation and pneumatonometric (limbal, sitting) IOP measurements (See Figure 1 for explanation).

Goldmann and pneumatonograph measurements were made by the same practiced examiner, but the pneumatonograph tracings were evaluated by a different investigator. A value was given for each tracing and none were discarded so that the worst case potential for variation was deliberately maximized. Each measurement was made without repetition.

Additionally, in a separate series of 65 eyes, pressure values for pneumatonograph measurements over the conjunctiva-sclera were recorded with the patient in the sitting position directly after Goldmann applanation in the same eye. In these examinations, the corneal extremity of the pneumatonograph sensor tip was 2 mm or more from the apparent corneoscleral limbus.

Statistical treatment:

1. For the determination of the relation between the various pneumatonograph and the Goldmann measurements, the following statistical methods were applied to the data:
   A. two-tailed, paired sample *t*-test;
   B. regression analysis;

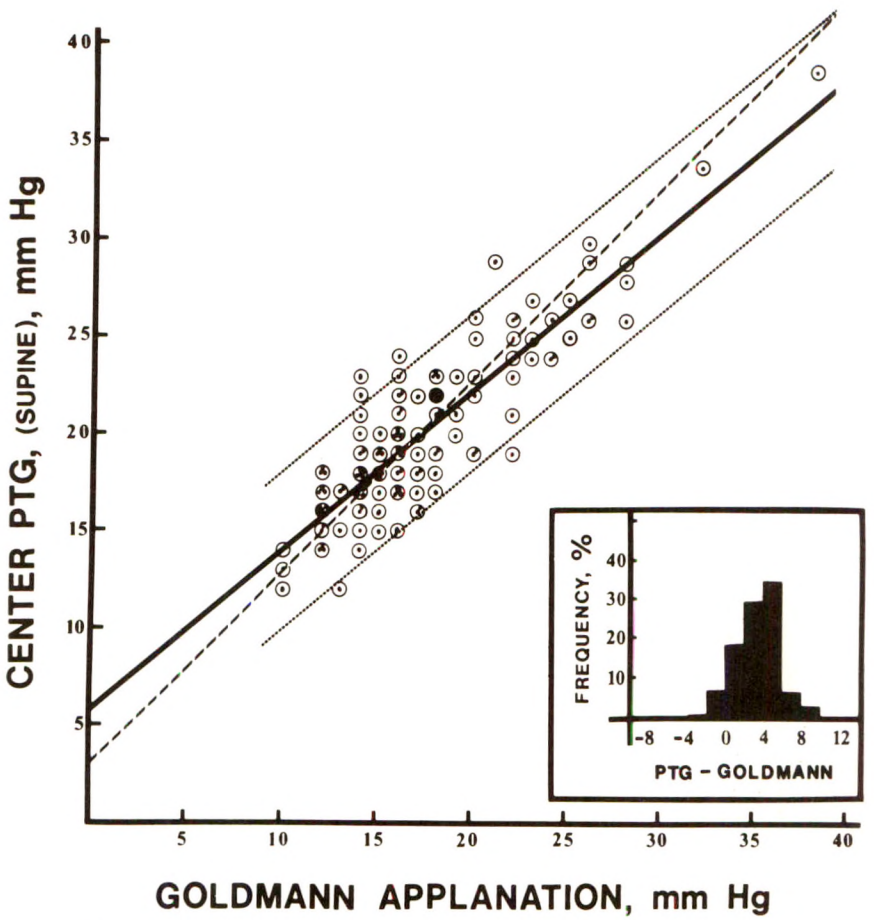

Fig. 3 (Breitfeller and Krohn). Relationship between applanation and pneumatonometric (central, supine) IOP measurements (See Figure 1 for explanation).

C. frequency distribution for the difference between measurements;
D. calculation of inverse prediction limits.

For this statistical treatment, the Goldmann values were taken as the independent variable and so assumed to be the true intraocular pressure. The inherent variation of the Goldmann measurements (as contrasted with direct manometry) is therefore artifactually attributed to the pneumatonometric method in this analysis.

2. Limbal pneumatonograph measurements were compared to central corneal pneumatonograph measurements, both in sitting and supine positions, by application of the same statistical methods as outlined.

Results

In the separate series of 65 eyes pneumatonograph conjunctival-scleral intraocular pressure measurements were, in all cases, higher than those made with the Goldmann instrument in the same eye. For this series, the mean Goldmann value was 20.1 mm Hg (5.8 S.D.), whereas that

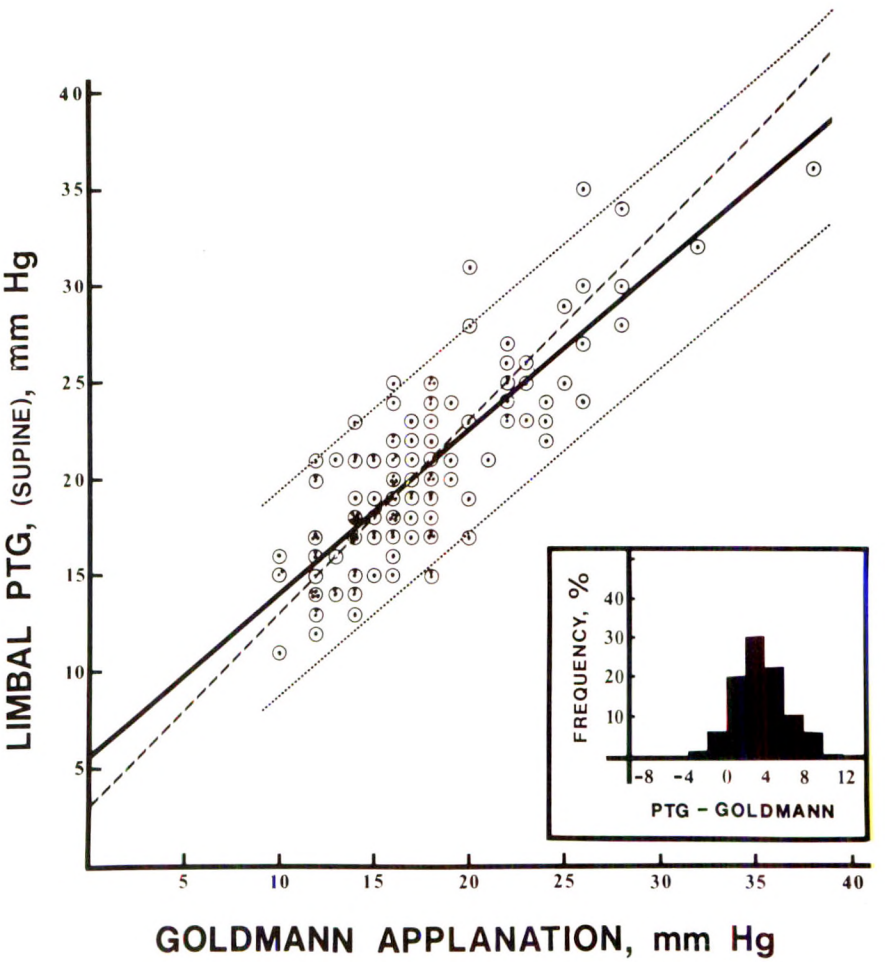

Fig. 4 (Breitfeller and Krohn). Relationship between applanation and pneumatonometric (limbal, supine) IOP measurements (See Figure 1 for explanation).

for pneumatonograph scleral measurements was 35.5 mm Hg (10.2 S.D.). Paired sample analysis showed no reliable correlation.

For the major series of 131 eyes, Table 1 shows the mean and standard deviation for each mode of intraocular pressure measurement. The mean pneumatonograph values are all higher than those found for Goldmann applanation. The relatively high standard deviations obscures the significance of these differences. However, a two-tailed, paired sample *t*-test for the difference between means (Table 2) shows the differences between each of the pneumatonograph modes and the Goldmann determinations to be highly significant. Also, the relatively small differences between the pneumatonograph sitting-center and pneumatonograph sitting-limbal measurements was statistically significant. In contrast, the supine pneumatonograph measurements at the center were not distinguishable from those at the corneoscleral limbus. (The frequency histograms inserted in Figures 1 to 6 show the relatively normal distribution of the differences between paired samples.) The regression analysis for each of the relationships between the

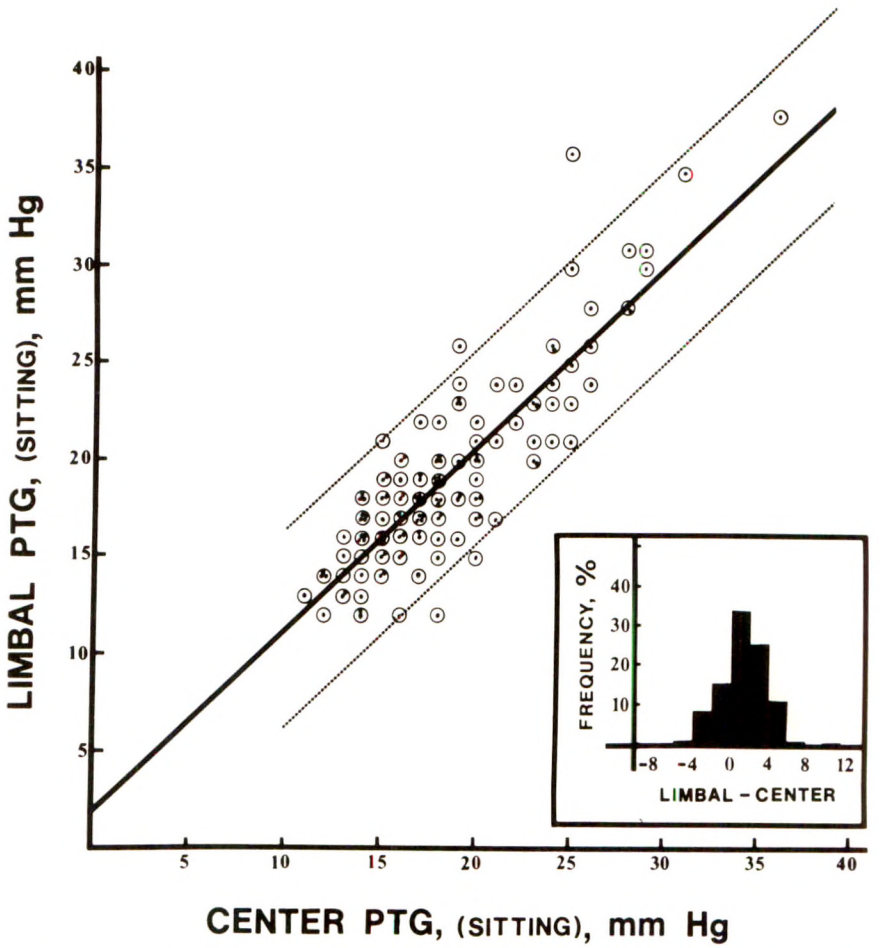

Fig. 5 (Breitfeller and Krohn). Pneumatonograph measurements on sitting subjects. Relationship between limbal and central (apical) values. Plot of paired measurements on the same eye: the number of dots within a circle indicates the number of values with the same coordinates; the solid straight line is the regression; the dotted lines are the 95% confidence limits for the prediction of central from limbal (inverse prediction). Histogram: the frequency distribution for the difference between limbal and central IOP values for the same eye.

various modes of measurement is shown in Table 3, which includes the correlation coefficients (R) indicating the linearity of the relationships in all cases. The relationships are depicted graphically in Figures 1 through 6. Inverse prediction limits to the 95% confidence level were calculated for the estimation of a Goldmann value corresponding to any single pneumatonograph measurement based on this data, which had been collected so as to imitate worst case clinical situations. For all comparisons with Goldmann values, a line having a slope of 1 and a positive unit Y-intercept was drawn that approximates the regression and falls within the inverse prediction limits. The Y-intercept of this line is designated as the Clinical Correlation Estimator.

Discussion

These findings indicate a clinically useful relationship between limbal pneumatonometry and Goldmann applanation to-

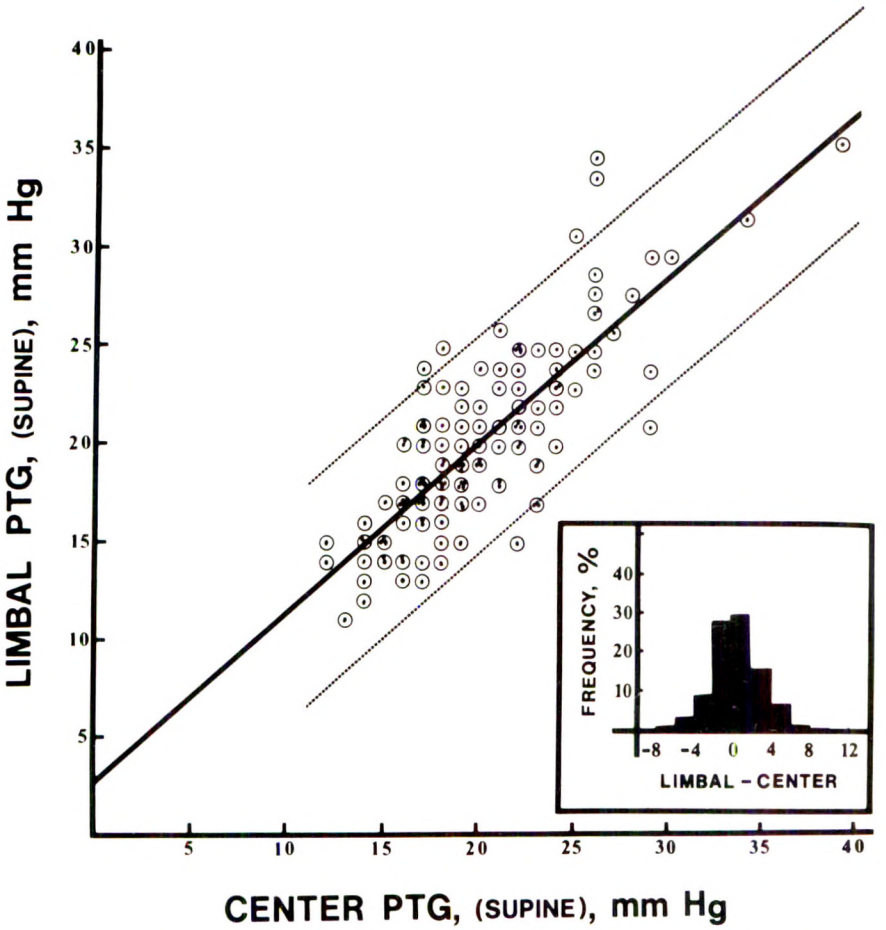

Fig. 6 (Breitfeller and Krohn). Pneumatonograph measurements on supine subjects. Relationship between limbal and central (apical) values (See Figure 5 for explanation).

nometry, despite a deliberate attempt in this study to maximize possible sources of variation, including the stipulation that a value was assigned to every pneumatonograph tracing, and the exclusion of opportunity to confirm readings by repetition. Under actual clinical conditions, much less scatter would be expected because only tracings of good quality would be acceptable and poor tracings would naturally be repeated.

The difference found between pneumatonograph center-sitting and conventional Goldmann applanation was comparable to that found by others.[2,3] The difference found in this study between central-sitting and central-supine by pneumatonograph was comparable to that found by Jain and Marmion,[4] but somewhat lower than that reported by Krieglstein and Langham.[5] To the best of our knowledge, there are no published reports of systematic use of the corneoscleral limbus as a tonometry site except for that of Wilke,[6] who found good correlation between central corneal and limbal or paralimbal measurements with use of a vibration tonometer. The difference be-

TABLE 3

REGRESSION ANALYSIS*

Modes of IOP Measurement	Slope	S_b	Y-intercept	R
Goldmann vs PTG, sitting, center	0.883	0.032	3.26	0.927
Goldmann vs PTG, sitting, limbal	0.886	0.048	4.02	0.850
Goldmann vs PTG, supine, center	0.830	0.038	5.80	0.886
Goldmann vs PTG, supine, limbal	0.846	0.051	5.67	0.827
PTG, sitting (center vs limbal)	0.943	0.049	1.87	0.862
PTG, supine (center vs limbal)	0.877	0.057	2.60	0.804

*PTG designates pneumatonograph.

tween measurements at the two sites was similar to that found in this study.

The results of our study show that intraocular pressure measurements on normal corneas by pneumatonometry performed with the sensor tip on the corneoscleral limbus or slightly corneal to this location are uniformly higher than standard Goldmann applanation pressures. This is true for a range of pressures extending from low normal to glaucomatous values.

Of clinical significance is that Goldmann pressures may be predicted from both central and limbal pneumatonograph measurements within clinically useful limits at the 95% confidence level by use of the Clinical Correlation Estimator. To estimate corresponding Goldmann applanation IOP values, the Clinical Correlation Coefficient is subtracted from the IOP value measured by using the following pneumatonograph modes: sitting, center, 1; sitting, limbal, 2; supine, center, 3; and supine, limbal, 3. If the patient is supine, there appears to be no statistically significant difference between the central and the limbal readings. This suggests that application of the pneumatonograph sensor tip to any disease-free area of the cornea, including the limbal and paralimbal areas, affords a reliable estimate of the intraocular pressure as measured by the familiar Goldmann applanation instrument, and that the supine position for pneumatonograph for measurements is optimal for this purpose.

The problem of tonometry in the presence of corneal disease or after keratoplasty has been approached with the use of various tonometers placed centrally.[7,8] For this application, the Mackay-Marg tonometer appears to date to have the best correlation with direct manometry.[9] Limbal pneumatonometry has not, as yet, been subjected to such testing.

SUMMARY

A series of comparisons in normal and glaucomatous eyes, all with normal corneas, was made between Goldmann applanation tonometry and Langham pneumatonometry, central and limbal, and with the patient in sitting and supine positions. All measurements were made at one visit with a standardized sequence. All mean pneumatonograph measurements were significantly higher than the corresponding applanation value. However, no significant difference was found between limbal and apical pneumatonograph values in the supine subject. Conversion values relating pneumatonograph measurements and applanation values have been derived and designated as Clinical Correlation Estimators. This allows prediction of Goldmann applanation values by extrapolation of limbal

pneumatonograph measurements at a 95% confidence level. The method has potential use in the determination of intraocular pressure in the presence of corneal disease.

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SECRETORY COMPONENT IN HUMAN OCULAR TISSUES

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Secretory IgA (s-IgA), the predominant class of immunoglobulin in secretory tissues and external secretions[1] such as human tears,[2] is composed of two 7S IgA molecules, one molecule of J chain, and one molecule of secretory component. Secretory component and s-IgA were identified in tears by Josephson and Weiner[3] and secretory component was identified in human lacrimal tissue by Franklin, Kenyon, and Tomasi.[4]

Using immunofluorescence techniques, we studied the cellular sites for the synthesis of secretory component in lacrimal glands, accessory lacrimal glands, and other ocular tissues. Based on these studies, we designed a model of the ocular secretory system; this model involves: (1) the synthesis of secretory component in lacrimal tissues (both main and accessory glands); (2) the absence of secretory component production in any other ocular tissues, including conjunctiva; and (3) the possible combination of dimeric IgA with secretory component within lacrimal tubules.

SUBJECTS

Immunohistochemical studies were performed on exenteration specimens obtained at autopsy from seven subjects with no known ocular disease (Table), on surgical biopsy specimens of lacrimal gland obtained at orbital surgery in three patients (Table), and on biopsy specimens of upper, lower, and bulbar conjunctiva obtained from 14 subjects. The conjunctival specimens were obtained from three patients with no ocular inflammatory disease, from seven with a variety of diseases including three with pemphigoid and one each with quiescent herpetic keratitis, atopic conjunctivitis, giant papillary conjunctivitis, and episcleritis, and from four autopsy cases.

For the exenteration specimens the globes were enucleated with a peritomy close to the corneoscleral limbus. The bulbar and palpebral conjunctiva along with the main and accessory lacrimal tissues were then excised en bloc from the orbit (Fig. 1). The postmortem period before exenteration and the clinical status of lacrimal tissue donors are shown in the Table.

Tissue specimens were fixed in 19 parts absolute alcohol to one part glacial acetic acid at room temperature for 48 hours, a modification of a technique described by Wolman and Behar.[5] The tissue was then dehydrated, embedded in degassed paraffin, sectioned at 4 μ and deparaffinated as described by Sainte-Marie.[6]

Tetramethyl rhodamine isothiocyanate (TRITC)-labelled goat antihuman secretory component and fluorescein isothiocyanate (FITC)-labelled rabbit antihuman secretory component were prepared as previously described.[7] The following reagents were obtained commercially: rabbit antihuman IgA and rabbit antihuman IgG (Cappel), rabbit antihuman lactoferrin and rabbit antihuman secretory component (Behring), and FITC-labelled goat antirabbit gamma globulin. Purity of antisera was tested by Ouchterlony analysis (Fig. 2).

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TABLE

LACRIMAL TISSUE DONORS

Case No.	Age (yrs)	No. of Hours After Death	Diagnosis
Tissue from autopsy			
1	54	22	Alcoholic cirrhosis of liver with jaundice
2	67	23	Severe rheumatoid arthritis; pneumonia; subacute bacterial endocarditis
3	72	20	Carcinoma pf pancreas with metastasis
4	73	22	Progressive supranuclear palsy
5	59	120	Cirrhosis; portal hypertension; no jaundice
6	65	9	Acute renal tubular necrosis with renal failure; Staphylococcus bacteremia
7	65	31	Pulmonary edema; second-degree cardiac failure
Tissue from surgery			
8	35	—	Thyroid exophthalmos
9	30	—	Epibulbar venous aneurysm
10	31	—	Thyroid exophthalmos

Tissue sections were stained with the three antisecretory component antisera. The TRITC-conjugated goat antisecretory component was used for direct immunofluorescence staining. Because FITC-labelled rabbit antisecretory component produced weak fluorescence, a second layer of FITC-labelled goat antirabbit gamma globulin was added. The unlabelled rabbit antisecretory component was also followed by FITC-labelled goat antirabbit gamma globulin. Sections were stained with each antiserum for 15 minutes at room temperature in a moist chamber, then rinsed twice in phosphate-buffered saline, pH 7.2, for five minutes.

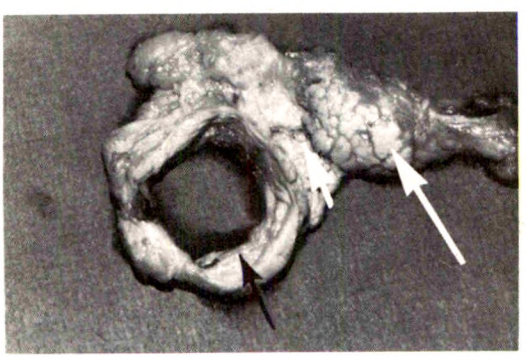

Fig. 1 (Allansmith and Gillette). Exenteration specimen. Note inferior forniceal conjunctiva (black arrow), one of many accessory lacrimal glands (short white arrow), and main lacrimal gland (long white arrow).

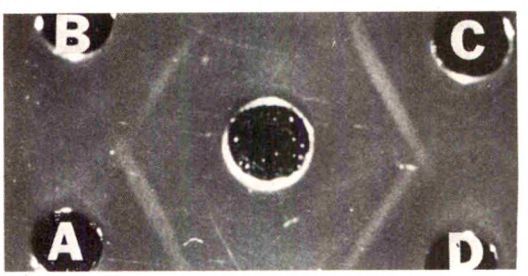

Fig. 2 (Allansmith and Gillette). Ouchterlony analysis of reagents. (A) Rabbit antilactoferrin; (B) rabbit anti-IgA; (C) rabbit antilactoferrin); (D) FITC-labelled rabbit antisecretory component. Human tears are in center well. Note lack of identity in lines from wells C and D showing that no antilactoferrin antibodies are in the rabbit antisecretory component reagent.

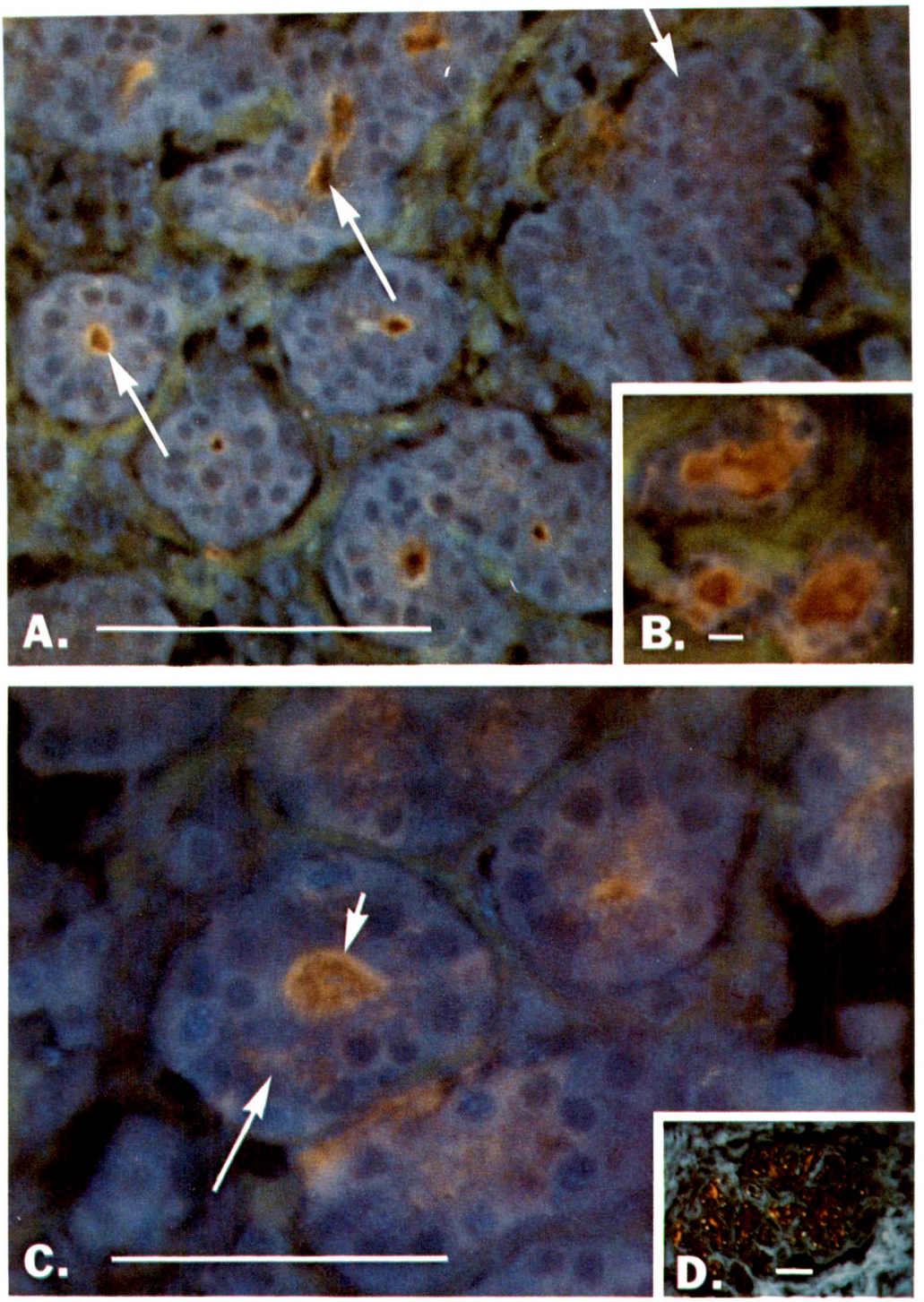

Fig. 3 (Allansmith and Gillette). Lacrimal glands stained with TRITC-labelled goat anti-secretory component. Orange indicates specific staining. Blue and green are auto-fluorescence. (A) Main lacrimal gland showing secretory component (orange material) in acinar lumina (long white arrows). Acini devoid of staining for secretory component are also shown (short arrow); bar gauge = 100 μm (x250). (B) Medium-size excretory tubules containing secretory component; bar gauge = 10 μm (x250). (C) High-power view of acini showing diffuse staining of cytoplasm (long white arrow and rimming of lumen (short white arrow); bar gauge = 50 μm (x1,000). (D) Accessory lacrimal gland. Note secretory component in acini and lumina; bar gauge = 100 μm (x100).

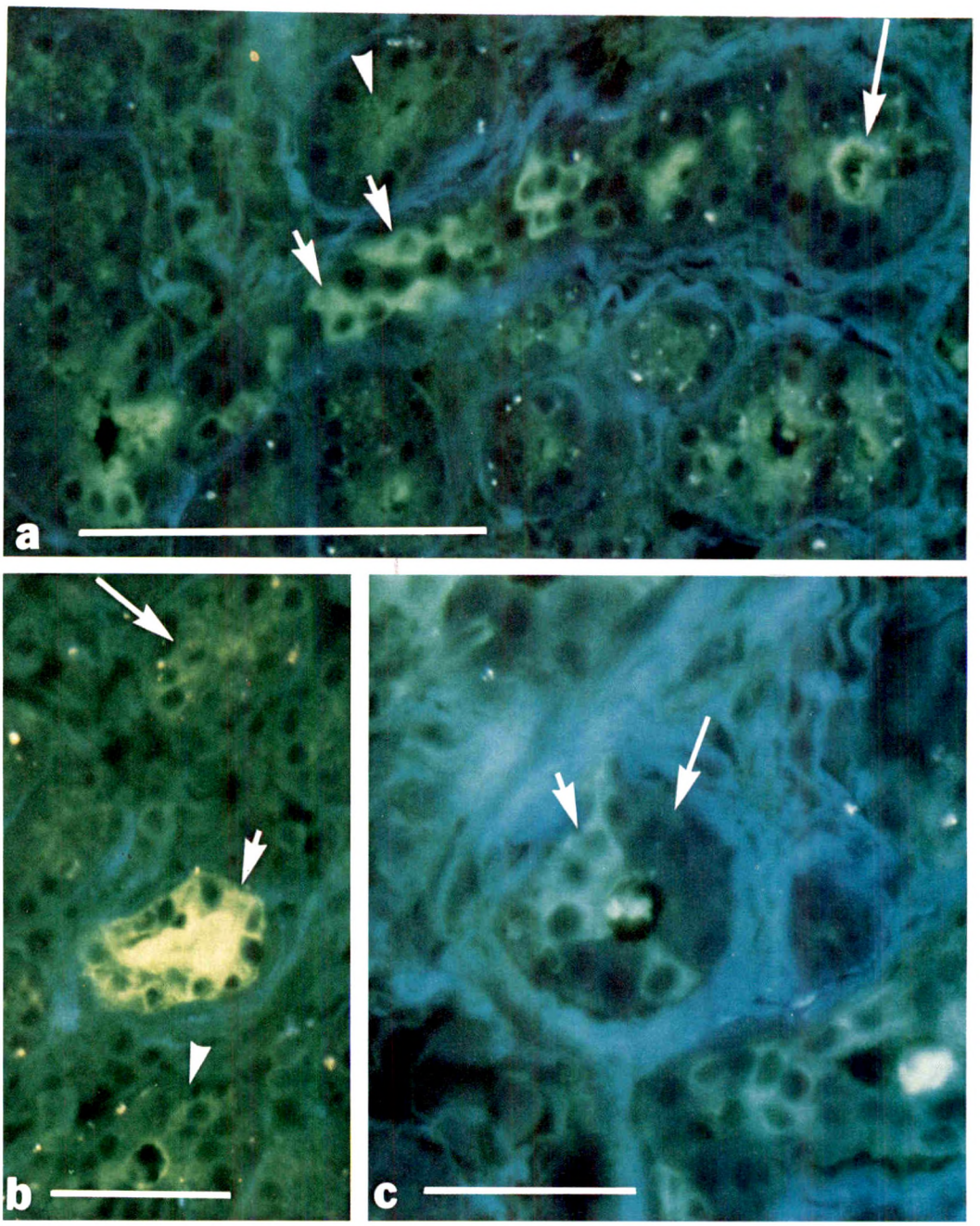

Fig. 4 (Allansmith and Gillette). Main lacrimal gland stained with rabbit anti-secretory component followed by FITC-labelled goat anti-rabbit IgG. Compare similarity of staining pattern with Figure 3. Green indicates stain for secretory component. Blue is autofluorescence. (a) Acinus with brightly staining rim of secretory component (long white arrow) leading into tubule with brightly staining cells (short arrows). Note diffuse staining for secretory component C (arrowhead); bar gauge = 100 μm (x250). (b) Small excretory tubule filled with secretory component (short white arrow) surrounded by brightly staining epithelial cells. Diffusely staining acinus without rim-staining of luminal surface is shown (long white arrow). Acinus with brightly staining luminar rim and little cytoplasmic staining is shown with arrowhead; bar gauge = 50 μm (x250). (c) Acinus with brightly staining cell (short arrow) adjacent to cell devoid of staining (long arrow); bar gauge = 50 μm .

Sections were mounted in buffered glycerol, pH 8.0, covered with a cover slip, and sealed with clear nail polish.

Control sections for TRITC-stained material were incubated with TRITC-conjugated antiserum to bovine serum albumin. Controls of sections for the indirect immunofluorescence technique using FITC label were incubated with normal rabbit serum followed by FITC-labelled goat antirabbit gamma globulin. An additional control for secretory component staining was the blocking of fluorescence by incubation of the tissues with unconjugated rabbit antisecretory component followed by rhodamine-conjugated goat antisecretory component.

Sections were examined with a Zeiss fluorescence microscope with 200-W high-pressure mercury vapor lamp, UG 5 exciter filter, and a 410-nm barrier filter for FITC and a 580-nm excitation filter with a 650-nm barrier for TRITC. Photographs for both fluorescein and rhodamine fluorescence were taken; fluorescein with the observation filter combination, rhodamine with a BG12 exciter filter, and 530-nm barrier filter combination. Ektachrome ASA 200 and ASA 400 color films were used.

Results

Antisecretory component antisera stained the secretory and tubular areas of all lacrimal tissues, but the pattern of staining differed for the two areas (Figs. 3 and 4). Staining of acini, identified by their small luminal diameter relative to epithelial circumference, was seen in approximately 60% of acinar cells. The intensity of staining ranged from barely perceptible (most cells) (Fig. 3) to extremely bright (about 5%). The differences in the intensity of staining may be attributed to a maturational difference rather than to a difference in cell type. Staining was seen both in basal and apical portions of the acinar cells, and acini were seen in which brightly staining cells were adjacent to negative cells (Fig. 4). Entire acini were seen that were completely devoid of staining (Fig. 3).

Acinar lumina often contained brightly staining material and the luminal rim exhibited a strong fluorescence (Fig. 3). This phenomenon was seen both in acini containing secretory component and in acini devoid of intracellular staining. No intercellular staining was detected.

The excretory tubules were identified by their larger luminal diameter relative to the epithelial circumference. The tubules ranged from those contiguous with acini and of one epithelial layer (Fig. 4) to large tubules distant from acini and of two or three layers of epithelium with no adjacent interstitial plasma cells (Fig. 5). In contrast to acinar cells, most staining

Fig. 5 (Allansmith and Gillette). Large excretory tubules of main lacrimal gland stained for secretory component. Note bright staining of many tubular cells (arrows), absence of plasma cells in interstitial areas around tubules, and nonstaining acini (arrowheads). Bright material in vessel (V) is autofluorescent; bar gauge-50 μm (×250).

tubular cells were brightly stained. Tubules were seen in which all epithelial cells stained brightly; this phenomenon was not seen in acini. Bright staining was seen in tubules of all sizes, ranging from those with a single layer of cuboidal epithelium (Fig. 3) to those composed of two or three layers of epithelial cells (Fig. 5). The staining pattern of some tubules was similar to that of some acini, in that cells without stain were adjacent to staining cells (Fig. 4). In general, approximately 30% of tubular cells stained brightly compared with approximately 5% of acinar cells. Some tubules were sectioned tangentially and showed positive staining of the epithelium throughout their length against a background of lesser-staining acini (Fig. 4).

Tubular lumina were often filled with intensely staining material (Figs. 3-5). This was usually found in conjunction with positively stained epithelial cells, although it was also seen in the presence of unstained tubular epithelial cells. No staining of interstitial tissues, vascular components, or lymphoid elements was seen, with the exception of interstitial staining in Case 1.

Accessory lacrimal glands exhibited a secretory component staining pattern identical to that of the main lacrimal glands (Fig. 3). Accessory glands were available only from autopsy cases.

All sections of conjunctiva examined, whether from biopsy or autopsy specimens, revealed no staining for secretory component within the epithelium or substantia propria (Fig. 6). Staining of a homogeneous material adherent to the conjunctival surface was seen in some specimens (Fig. 6, inset). No staining for secretory component was observed in the cornea, iris, choroid, retina, sclera, episclera, extraocular muscles, or orbital fat.

A 54-year-old man had alcoholic cirrhosis (Case 1, Table) and was deeply jaundiced at the time of death. The interstitial tissue stained moderately for secretory component with all three antisera. The stained material was diffuse and differed notably from tissues of the other nine subjects.

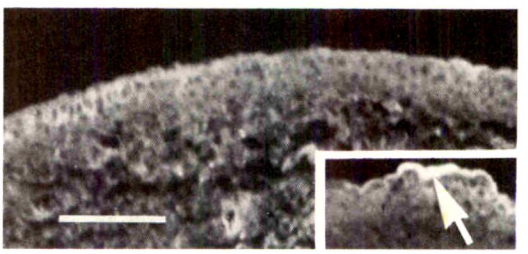

Fig. 6 (Allansmith and Gillette). Conjunctiva stained for secretory component. Note absence of specific staining in epithelium and substantia propria. Staining was occasionally seen on the surface that corresponded to mucus layer (arrow); bar gauge-50 μm (×250).

Discussion

Areas of the normal human eye that are associated with large accumulations of plasma cells adjacent to epithelial mucosal surfaces include conjunctiva, lacrimal gland, and accessory lacrimal glands.[8] Those areas that contain secretory component are also potential sites for synthesis of s-IgA.

Our results confirm those of Franklin and coworkers[4]; secretory component is produced in the human lacrimal gland. This study extends their work in describing that over 60% of the acini stain for secretory component. With stronger antisera, staining might be even greater. In about 5% of the cells, secretory component within the acinus was at such a level as to stain brightly. We add the previously unreported finding that tubules stain brightly for secretory component, which indicates that they might be a site for the production of secretory component, and that accessory lacrimal tissue forms secretory component.

Possibly, the large amount of secretory

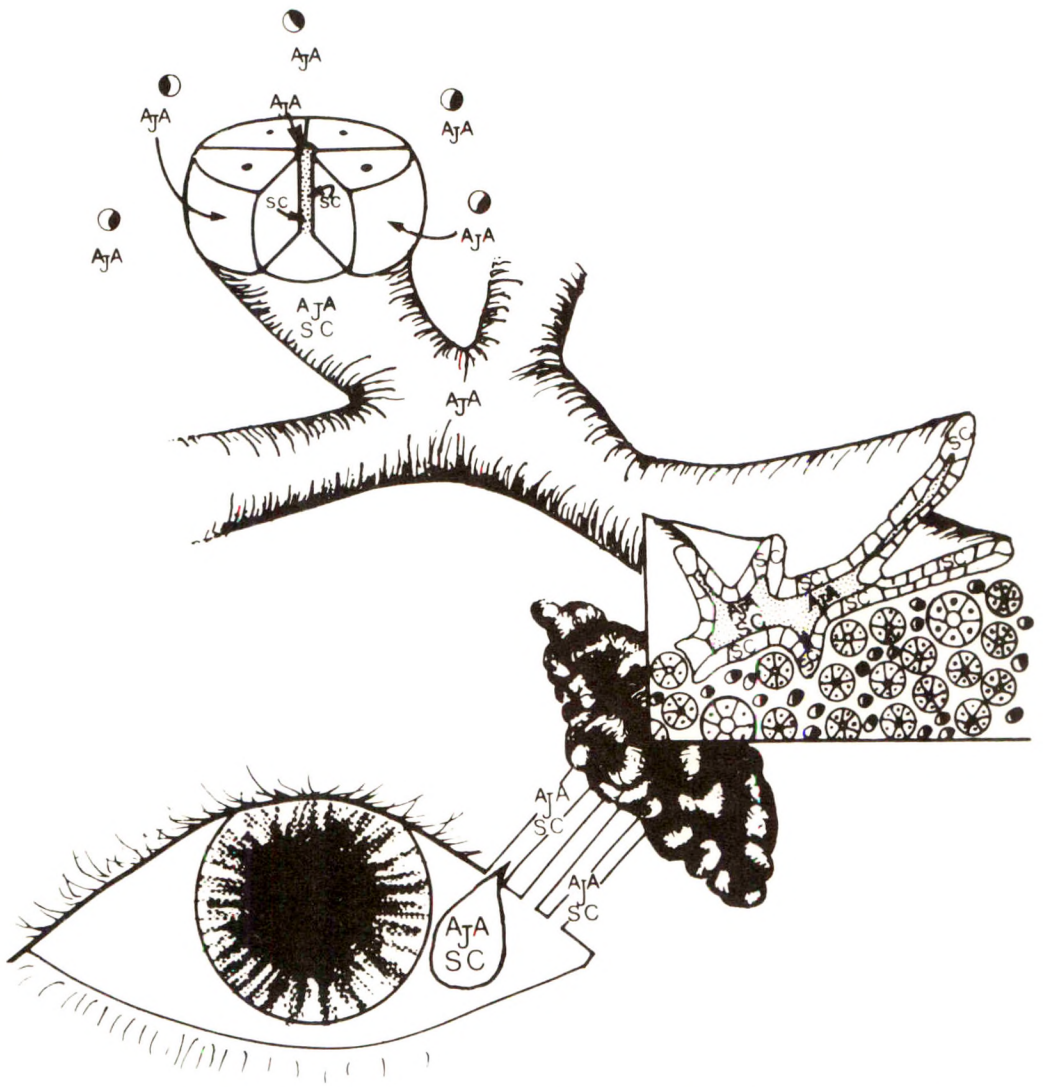

Fig. 7 (Allansmith and Gillette). Diagrammatic representation of secretory component formation in lacrimal glands. Dimeric IgA coupled with J chain (A-J-A) is formed by plasma cells in interstitial tissues of main and accessory lacrimal glands. This molecule is combined with acinar-produced secretory component to make s-IgA, which is excreted into lumen. A small amount of dimeric IgA free of secretory component is excreted into lumen. Free secretory component is also excreted by tubules into lumen to create relative excess of secretory component that combines with luminal dimeric IgA; s-IgA flows onto all areas of ocular surface.

component found in tubular cells combines with free dimeric IgA intraluminally. A similar distribution of cells that secrete a high level of secretory component in the tubules as compared with the acini was noted also in the mouse submaxillary gland.[9] Intraluminal combination of dimeric IgA with secretory component was also suggested for this system. A schematic representation of our concept of the ocular s-IgA system is presented in Figure 7.

Excretory tubules contain secretory component (Fig. 5) but lack secretory

granules,[10] which precludes the presence of secretory component in these granules. Whereas Franklin and co-workers[11] reported the presence of secretory component in the rabbit conjunctiva, we were unable to detect secretory component in human conjunctiva. This discrepancy may result from an interspecies difference.

Franklin (personal communication, 1978) reported that human autopsy material stained irregularly, whereas surgical material showed secretory component more reliably. The report of Franklin and associates was based on lacrimal specimens from surgery. Although most of our tissues were obtained from autopsies (Table), the staining patterns were identical for tissues from the two sources. The autopsy specimens were preferable because they allowed examination of more areas.

A crucial aspect of the localization of secretory component is the antisera used. Lactoferrin is difficult to separate from secretory component, and antilactoferrin antibodies therefore often contaminate secretory component antisera.[1] The lack of antilactoferrin antibody in our preparations was shown for each antiserum by Ouchterlony analysis (one example shown in Figure 2).

The high level of secretory component observed within the ducts might have been caused by the absorption of secretory component from the lumen into the cells lining the tubules. This possibility was excluded as we observed some tubules, large and small, that had highly staining luminal material within but no staining of adjacent epithelial cells (Fig. 3).

Case 1 had alcoholic cirrhosis with jaundice, and secretory component has been recorded to increase an average of sixfold in the serum of persons with cirrhosis.[12] This patient exhibited secretory component in interstitial spaces of lacrimal glands. Possibly, in Case 1 (Table), secretory component may have been present in the serum at a level sufficient to cause interstitial staining.

We conclude that the sites of secretory component manufacture around the eye are the acini of the main and accessory lacrimal glands and the excretory tubules of lacrimal tissue. We also conclude that, in the human, the conjunctiva and other ocular and periocular tissues do not stain for secretory component by the techniques used.

Summary

Lacrimal tissue and accessory lacrimal tissue from seven autopsy cases, lacrimal tissue from three patients undergoing orbital exploration, and biopsy specimens from conjunctiva of 14 subjects were examined for the presence and distribution of secretory component by three anti-secretory-component antisera. Secretory component was present in all lacrimal and accessory lacrimal tissues but in no other ocular tissues. Over 60% of acinar cells stained for secretory component; about 5% of acinar cells stained brightly; about 30% of tubular cells stained brightly. Main and accessory lacrimal tissues appeared identical in their staining patterns.

We concluded that the main sites of synthesis of secretory IgA in human ocular tissues are the lacrimal and accessory lacrimal tissues.

Acknowledgments

Richard Dallow, M.D., provided surgical specimens and Sylvia Crago, M.D., and Jiri Mestecky M.D., provided antisera.

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Fifty years ago this month in The Journal:

In the whole field of ophthalmic surgery, no maneuver calls for greater delicacy of touch than this grasping of a delicate anterior capsule with the intent to employ that capsule as a means of traction upon the suspensory ligament. Failure, in properly selected cases, may depend first upon attempting too large a grasp upon the anterior capsule, second upon holding the fold of capsule too firmly, and third upon using traction too brusquely.

Intracapsular extraction, By W. H. Crisp
Am. J. Ophthalmol. 13:244, 1930

CHOROIDAL VASCULAR CHANGES IN TOXEMIA OF PREGNANCY

DAVID M. FASTENBERG, M.D., CARL L. FETKENHOUR, M.D., EARL CHOROMOKOS, AND DAVID E. SHOCH, M.D.

Chicago, Illinois

Toxemia of pregnancy is a syndrome of hypertension, proteinuria, edema, and weight gain. Clinically preeclampsia is the development of hypertension beyond the 24th week of gestation. There is usually associated proteinuria, but the amount is variable. Page and Christianson[1] stated that generalized edema may or may not be present and should not be required for the diagnosis because its occurrence does not affect perinatal outcome. They furthermore stated that the mean arterial pressure, which is defined as the sum of twice the diastolic pressure plus systolic divided by three, is an important factor to monitor when placing the patient in a specific diagnostic category.

Pritchard[2] defined preeclampsia as pregnancy-induced hypertension occurring without preexisting vascular disease. When underlying chronic vascularity is present he termed this preeclampsia superimposed on chronic hypertension. Eclampsia exists when the pregnancy-induced or aggravated hypertensive state induces convulsions. Other associated findings with toxemia include hyperreflexia, oliguria, and cerebral and visual disturbances.

Most of the ocular complications in toxemia of pregnancy are found in the retina. These changes are associated with vascular hypertension and include retinal angiospasm, multiple hemorrhages, cotton-wool exudates, optic atrophy, and exudative retinal detachments. It has been generally accepted that the retinal blood vessels decompensate, and are the primary cause of the fundus abnormalities.[3]

Since the development and widespread clinical use of fundus photography and fluorescein angiography, others[4,5] have suggested that choroidal abnormalities may be responsible for some of the retinopathy seen in toxemia, specifically the secondary retinal detachments.

We examined a group of patients with toxemia of pregnancy and photographed the ocular fundus in those showing ophthalmoscopic abnormalities. Fluorescein angiography was used to help study the retinal and choroidal vasculatures as well as the retinal pigment epithelium. By the use of this angiographic technique we hoped to definitely implicate one or the other of the two vascular systems in the eye.

SUBJECTS AND METHODS

Twenty-seven patients with toxemia of pregnancy, first seen from two days to two months after delivery, were examined with indirect ophthalmoscopy and contact lens biomicroscopy. Five of these patients had abnormal fundi and were additionally studied with stereoscopic color photography and fluorescein angiography. Prepartum angiography was deferred because of potential toxicity to the newborn.

CASE REPORTS

Case 1—A 35-year-old woman, prima gravida, had toxemia of pregnancy characterized by a history of seizures, severe headaches, episodes of bilateral amaurosis, hypertension, and proteinuria. Two days after delivery, she complained of blurred vision. Visual acuity was 6/24 (20/80) in each eye. Blurred disk margins, retinal edema in the posterior pole, and retinal striae were present in both fundi.

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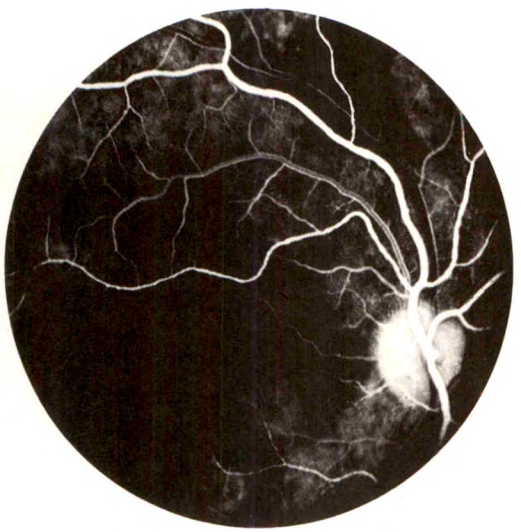

Fig. 1 (Fastenberg and associates). Case 1. Early fluorescein angiography of right eye showing choroidal nonfilling.

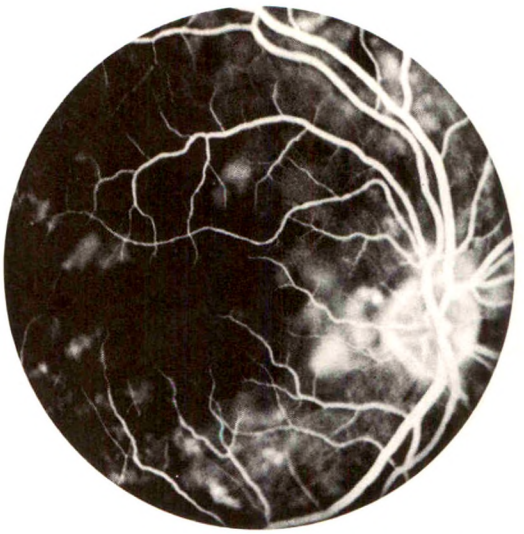

Fig. 2 (Fastenberg and associates). Case 1. Mid-phase fluorescein angiogram of right eye showing persistent choroidal nonperfusion and hyperfluorescence.

Yellow-white foci lying deep within the retina were seen in the peripapillary and macular areas. No retinal hemorrhages were evident. The retinal blood vessels showed no evidence of angiospasm. Fluorescein angiography showed areas of choroidal nonfilling with late fluorescein extravasation into subretinal and subpigment epithelial spaces (Figs. 1 to 3).

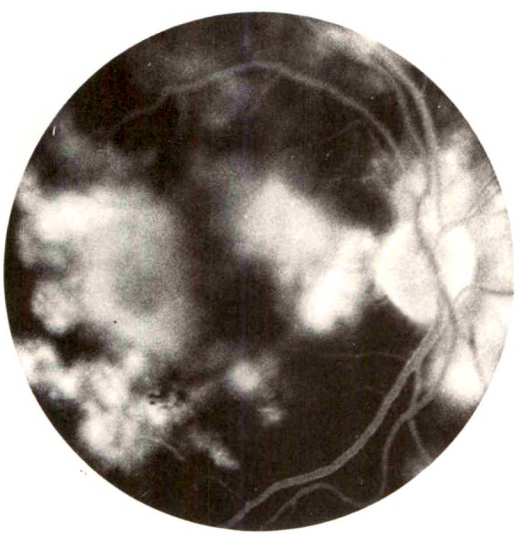

Fig. 3 (Fastenberg and associates). Case 1. Late-phase fluorescein angiogram of right eye showing extravasation of dye into subpigment epithelial and subretinal spaces.

Case 2—A 34-year-old woman, gravida 11, para 7, abortion 4, who had a history of essential hypertension, was followed up for increasing weight gain, proteinuria, and edema. Her blood pressure on examination was 190/120 mm Hg. After a seizure the patient complained of an episode of bilateral amaurosis. Two days after delivery, she complained of blurred vision in each eye. Her visual acuity was 6/18 (20/60) in each eye. Diffuse retinal edema in the posterior poles with blurred disk margins and retinal striae were observed in both fundi. The retinal blood vessels showed no angiospasm. Deep retinal yellow-white foci were seen at both posterior poles (Figs. 4 and 5). Fluorescein angiography showed areas of choroidal nonfilling with extravasation of dye into subretinal and subpigment epithelial spaces (Figs. 6 and 7). A follow-up examination seven months later revealed areas of retinal pigment epithelial hyper- and hypopigmentation and the presence of the underlying choroidal fluorescence (Fig. 8).

Case 3—A 24-year-old woman, prima gravida, was admitted for increasing weight gain, proteinuria, and edema. Blood pressure was 160/100 mm Hg. After delivery, she complained of blurred vision in each eye. Her visual acuity was 6/7.5 (20/25) in each eye. Edema of both posterior poles was noted. The retinal vessels showed no angiospasms. Fluorescein angiography showed areas of leakage of dye into the retina from choroidal vessels.

Case 4—A 27-year-old woman, prima gravida, who had a history of toxemia of pregnancy was seen in the eye clinic for a routine follow-up examination one month after delivery. Her visual acuity was 6/6 (20/20) in each eye. Ophthalmoscopic examination

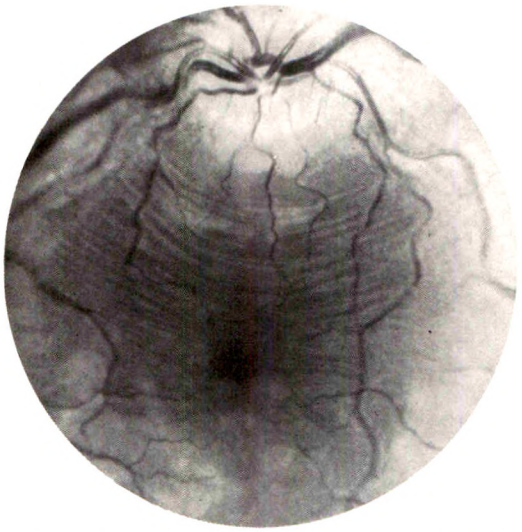

Fig. 4 (Fastenberg and associates). Case 2. Left eye showing blurred disk margin, retinal edema, and striae.

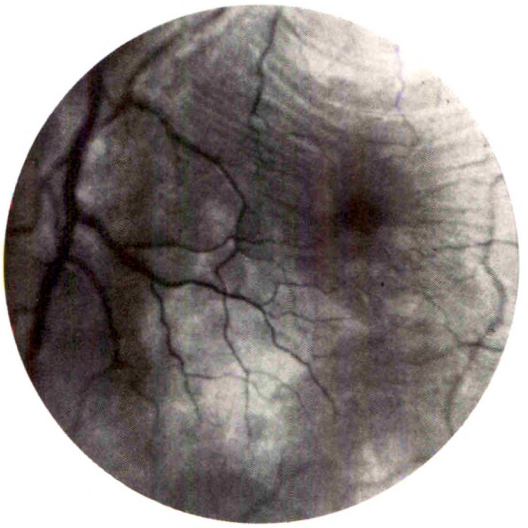

Fig. 5 (Fastenberg and associates). Case 2. Left eye showing deep retinal yellow-white foci.

was normal with the exception of areas of pigment epithelial derangement throughout the posterior poles. Fluorescein angiography showed areas of hypopigmentation and the presence of the underlying choroidal fluorescence.

Case 5—A 26-year-old woman, prima gravida, who had toxemia of pregnancy, was referred to us by another ophthalmologist. He found that she had inferior bullous retinal detachments both before and after delivery. We saw the patient two months after delivery. At that time her visual acuity was 6/9 (20/30) in both eyes, and her retinas were flat. Diffuse mottling and thinning of the pigment epithelium were evident. Fluorescein angiography showed many small areas of hypo- and hyperpigmentation and the presence of the underlying fluorescence. The retinal vasculature was normal. (Fig. 9).

Discussion

The relationship of choroidal changes and retinal detachment in toxemia of pregnancy was first described by Verdehame[6] in 1911. He showed choroidal scle-

Fig. 6 (Fastenberg and associates). Case 2. Early fluorescein angiogram of left eye showing multiple areas of choroidal nonfilling.

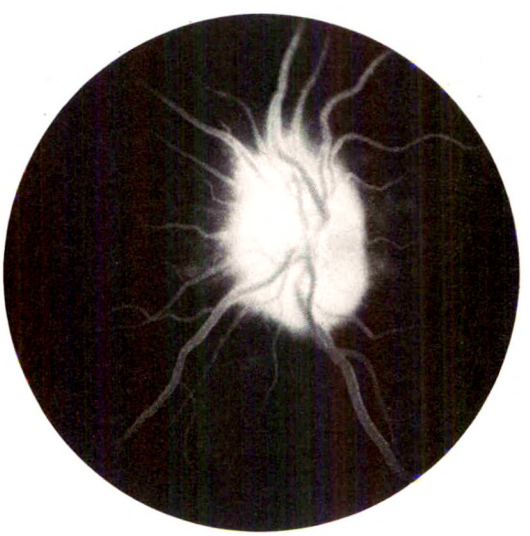

Fig. 7 (Fastenberg and associates). Case 2. Late fluorescein angiogram of left eye showing disk leakage and focal hyperfluorescence corresponding to yellow-white foci.

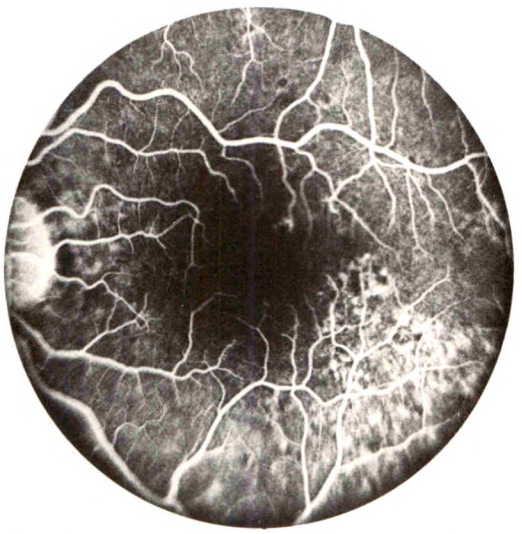

Fig. 8 (Fastenberg and associates). Case 2. Late fluorescein angiogram eight months later showing disturbance of retinal pigment epithelium and presence of dye.

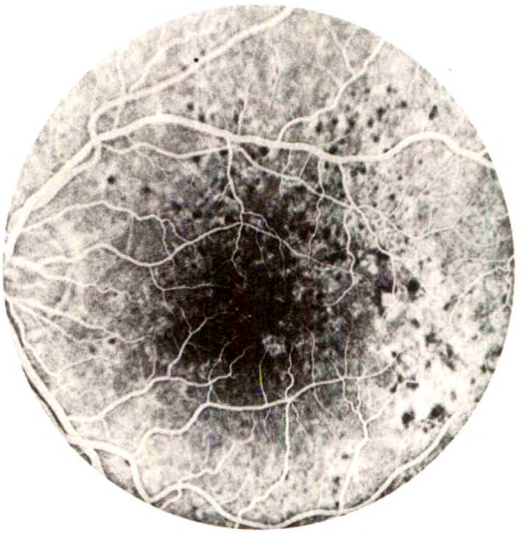

Fig. 9 (Fastenberg and associates). Case 5. Mid-phase fluorescein angiogram of left eye two months postpartum showing retinal pigment epithelial disturbance and presence of underlying fluorescence.

rosis in a postmortem examination of an eye of a woman who had had toxemia of pregnancy and secondary retinal detachment one year earlier. Other investigators[7–9] reported that the choriocapillaris and retinal pigment epithelium played a pathogenic role in the development of the retinal detachment. Ballantyne and Michaelson[10] suggested that the subretinal exudate causing the detachments originated in the choroid. Histologically, they showed cellular infiltrates in the choroid and retinal pigment epithelial disturbance. Gitter and associates[4] described multiple cyst-like elevations in the posterior pole of a toxemic patient, which leaked dye on fluorescein angiography from the choroid into the subretinal space. These investigators agreed with Collier[11] who believed that this dye leakage was caused by increased pressure in the choroidal vessels with subsequent transudation of fluid into the subretinal space. Kenney and Cerasoli[5] reported a case of toxemic retinal detachment with associated retinal vascular abnormalities and suggested that an insult to the choroidal vasculature caused choroidal detachments and retinal pigment epithelial damage.

Fluorescein angiographic findings in Cases 1 and 2 of our study support these findings. Choroidal nonfilling or nonperfusion is the angiographic equivalent of choroidal ischemia and could be responsible for the decompensation of overlying retinal pigment epithelium with leakage of dye into subpigment and subretinal spaces. Choroidal nonperfusion appeared as dark geographic areas of variable size and shape, most distinct as dye first entered the choroid. These areas eventually filled in as dye extravasated from the surrounding choriocapillaris. The retinal pigment epithelium overlying portions of these areas initially obscured the underlying fluorescence, and then stained heavily with leakage into the subretinal and subpigment epithelial spaces. The areas that sequentially obscured, stained, and leaked corresponded exactly to the yellow-white lesions seen ophthalmoscopically. These areas were similar to those that Gitter and associates[4] de-

scribed as "multilocular cyst-like elevations of the retina." These angiographic nonfilling areas should not be confused with patchy choroidal filling,[12] because there was a distinct absence of choroidal fluorescence for more than five seconds.

Clinical investigation of the fundus changes seen in toxemia of pregnancy have been augmented by a number of animal studies.[11–14] Choroidal ischemia was produced by a variety of experimental methods and then studied angiographically and histopathologically.[13,14] In all of the previously described studies a prominent angiographic finding was focal areas of abnormal retinal pigment epithelial permeability corresponding to yellow-white patches seen ophthalmoscopically in the outer retina.

There are similarities between the experimentally induced lesions of choroidal ischemia produced in the studies of Stern and Ernest[13] and Hayreh and Baines[14] with those we observed clinically in our Cases 1 to 3. These investigators on histopathologic examination showed necrosis and edema of the outer retinal layer, retinal pigment epithelial abnormality, and focal detachments associated with underlying areas of choriocapillaris occlusion. In our clinical series retinal pigment epithelial changes, visible ophthalmoscopically, in Cases 2, 4, and 5 correlated well with animal angiograms of Stern and Ernest[13] and Hayreh and Baines[14] that were performed two months after experimental choroidal infarction. These areas showed transmission of underlying choroidal fluorescence, and corresponded to regions of outer retinal infarction in which there was a loss of pigment granules.

Patients with toxemia of pregnancy are by definition hypertensive. The relationship of toxemia of pregnancy, retinal detachment, and hypertension may be better understood in light of several important studies. Stern and Ernest[13] produced secondary retinal detachments in animals by causing choroidal infarctions and then inducing systemic hypertension. Ischemic infarcts in the choriocapillaris in patients with retinal detachment and malignant hypertension had previously been shown by Klien.[15] Histopathologically, she found a relationship between the infarcted choriocapillaris and the subretinal transudates that produced the retinal detachments, and concluded that fluid entered the subretinal space through necrotic retinal pigment epithelial cells. We believe these experiments serve as excellent models for showing the pathogenesis of the retinal detachments seen in toxemia.

The predominant location of the fundus lesions in the posterior pole in our patients paralleled another of the experimental animal findings. In the choroidal nonperfusion experiments of Alm and Bill,[16] no major deficits were detected in the retinal periphery. Radioactive labeled microspheres injected into the ciliary vessels were heavily concentrated in the posterior pole. Stern and Ernest[13] believed that this was caused by the number of large diameter ciliary vessels that pierced the sclera in the macular area. Weiter and Ernest[17] and others[14,18,19] showed that the most dense portion of the choriocapillaris was located in the posterior pole. These studies stimulated a number of important considerations. Potts[20] reported that the concentration of vessels resulted in increased blood flow and pressure to the macular circulation. Stern and Ernest[13] speculated that this increased vascularity predisposed the area to occlusive phenomenon. Cogan[21] discovered a predilection for thrombi in the submacular choroid in postmortem eyes in patients with disseminated intravascular coagulopathy. He suggested that clots were precipitated by the rapid deceleration in flow as high speed arterial blood moved into the vast network of choroidal capillaries.

We hypothesize that the choroidal vascular insufficiency, which we believe is the causal factor in the development of the retinal detachments seen in toxemia, can develop as the result of two factors, either working together or independently. The first deals with the possibility of the development of emboli that originate in the products of conception. Beer[22] discussed the antigenic nature of the products of conception as the focus of an immune attack. Immune vasculitis can result in lipid accumulation, fibrin deposition, and ultimately occlusion of some of the placental vessels. This further leads to release of tissue thromboplastin, fibrin-fibrinogen and subsequent deposition elsewhere in the body (choroid).

Ocular blood flow is known to be affected by sympathetic nerve stimulation and systolic hypertension. Choroidal blood flow was increased after ocular sympathectomy, but this did not result in subsequent leakage of dye from the choroidal vessels.[23,24] Similarly, there was no leakage from the choroid in experimental animals subjected only to transient increases in systolic blood pressure.[25] However, when sympathectomy and hypertension were combined in the same animal, fluorescein readily leaked from the choroidal circulation into the retina.[25] Conversely, stimulating the ocular sympathetic nervous system in hypertensive cats prevented dye from leaking out of the uveal vessels.[26] We thus can hypothesize that transient derangements in the ocular sympathetics, in a patient with toxemic hypertension, can alter choroidal blood flow causing ischemia and the subsequent clinical appearance.

Although other investigators reported both retinal[5] and choroidal vascular abnormalities in toxemia of pregnancy, findings in our patients support the observation that choroidal rather than retinal blood vessels are primarily and predominantly involved in the pathogenesis of secondary retinal detachments. We found no evidence, either ophthalmoscopically or angiographically, of retinal vascular decompensation. The peripapillary retinal edema in Cases 1 and 2 originated from profuse leakage of the optic disk and not from retinal vessels. Because these patients were examined two days after delivery, possibly prepartum retinal vascular changes had cleared spontaneously. Even though retinal angiospasm might have disappeared rapidly, it would be unlikely that cotton-wool spots, hemorrhages, exudates, and vascular sheathing would resolve without a trace in such a short time.

Our findings on fluorescein angiography and color photography present a detailed description of choroidal vascular insufficiency. This was manifested by choroidal filling defects, retinal pigment epithelial damage, fluid transudation, and focal retinal detachments. The location and figurations of the fluorescein angiographic defects correlated well with those lesions seen on ophthalmoscopy and color photography. Although choroidal vascular abnormalities in toxemia of pregnancy is not a new concept, it has not been widely recognized. Many ophthalmologists continue to believe that retinal vasculature malfunctioning is primarily and solely responsible for the well-known fundus appearance, particularly secondary retinal detachments. In our series of patients there was evidence of secondary retinal detachments with no significant retinal vasculature changes. Changes attributed to choroidal insufficiency were frequent.

SUMMARY

Twenty-seven patients with toxemia of pregnancy were examined during a postpartum period of two days to eight months. Five of these manifested abnormal photographic and angiographic findings including disk and retinal ede-

ma, retinal striae, deep retinal yellow-white focal lesions, choroidal nonfilling, leakage of dye from the optic disk and deep retinal lesions, and retinal pigment epithelial window defects. The location and configuration of the leakage correlated with the defects seen on color photography. The normal retinal, and predominantly abnormal choroidal vascular patterns provide evidence implicating choroidal vascular insufficiency as the primary basis for secondary retinal detachments seen in toxemia of pregnancy.

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BASAL PRECORNEAL TEAR TURNOVER IN THE HUMAN EYE

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Maintenance of a normal rate of tear production and elimination by the lacrimal system is essential for the proper controlled environment for the cornea and the conjunctiva. Several clinically useful methods of measuring tear flow or tear turnover have been described and the results of studies using these tests have characterized the physiology of the normal eye.

Schirmer[1] first estimated tear flow to be from 0.6 to 0.8 μl min^{-1}, measuring the time required to produce epiphora in patients with obstruction of the lacrimal drainage system. He also devised a test to measure tear flow by placing a strip of filter paper in the tear film. Kirschner[2] instilled fluorescein indicator into the conjunctival sac, measured the fluorescence of samples, and found values for tear flow close to those reported by Schirmer. Mishima and associates,[3] by using a quantitative fluorophotometer to determine fluorescein concentration in situ, measured the disappearance of this tracer from the lower marginal tear strip. The physiologic tear flow was 1.2 μl min^{-1} with a range from 0.5 to 2.2 μl min^{-1}. The turnover rate was about 16% min^{-1}. No significant difference was found by Mishima and associates[3] between younger and older subjects. Sorenson[4] measured tear flow to be 0.6 μl min^{-1} using a technetium 99 tracer and a gamma counter. Both Mishima and associates[3] and Sorenson[4] emphasized that measurements of tear flow must be made without causing reflex lacrimation, one of the drawbacks of the Schirmer test. Mishima and associates[3] have shown that instillation of as little as 1 μl of an indicator solution can cause reflex lacrimation in some eyes for as long as five minutes.

The purpose of this study was to devise a clinical test for measuring basal tear flow in the unanesthetized human eye and to study the behavior of the normal human eye under the conditions of the test. It was intended that the test be quantitative, that it stimulate reflex tearing as little as possible, and that it be simple enough to be performed by an ophthalmic technician after a short instruction period. We chose a method patterned after that of Mishima and associates.[3]

SUBJECTS AND METHODS

Fifty-two normal volunteers were studied. Of these 52, 51 underwent a single determination of tear turnover in each eye and one subject underwent six determinations on successive mornings.

Volunteers were examined with a slit lamp to assure that the corneal epithelium and the lacrimal apparatus appeared normal, and that there was no staining of the cornea with fluorescein. Contact lens wearers were included but were instructed to remove their lenses at least one hour before the experiment. A standard formulation of sterile 10% sodium fluorescein solution was used as an indicator, and a slit-lamp fluorophotometer, described by

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Brubaker and Coakes,[5] was used for measuring fluorescein mass in the central zone of the precorneal tear film.

The excitation and measurement field sizes were 5 mm in diameter. The excitation beam was aligned along the optic axis, and the observation angle was set at 10 degrees to the observer's left. The magnification of the slit lamp was set at 40×. The slit lamp was centered and focused on the first Purkinje-Sanson image of the background lamp filament.

The subject was seated in front of the fluorophotometer, and three measurements of background fluorescence were made from each eye before fluorescein instillation. At time zero, 1 μl of 10% fluorescein was instilled into the lower conjunctival sac of the right eye. One minute later, 1 μl of the fluorescein solution was instilled into the left conjunctival sac. The subject was then instructed to blink at least three times to distribute the fluorescein throughout the tear film. Fluorescence measurements were made in each eye at five-minute intervals for 45 to 60 minutes. Each measurement was preceded by a blink and a delay of two seconds to allow the thickness of the precorneal tear film to stabilize. In a few subjects with rapid rates of turnover, more frequent measurements were made to insure an adequate number of values. The background value was substracted from each fluorescent measurement. The net fluorescence of the precorneal tear film, as a function of time, was studied and analyzed. These data were plotted on semilogarithmic graph paper until a portion of the plot appeared to be decreasing linearly. The data from the linear portion of the curve were fit by the method of least squares to an equation of the form:

$$F(t_2) = F(t_1)e^{-K_e(t_2-t_1)}$$

where *F(t)* is the net fluorescence of the central precorneal tear film at time *t*, and K_e is the tear elimination coefficient, expressed as percent per minute.

The precision of the test was determined from the single subject who was studied on six successive days. These six determinations were performed without physician assistance by an ophthalmic technician after a short instruction period. In this subject, the fluorescein was not applied quantitatively, but was simply applied to the lower tarsal conjunctiva with a moistened fluorescein paper strip. The tear elimination coefficient was calculated from the least squares exponential fit to the fluorescein data obtained at 15, 20, 25, and 30 minutes.

Results

The subjects were divided into three groups on the basis of their fluorescence decay curves. Group 1 consisted of 15 subjects who eliminated the dye completely in at least one eye by 30 minutes (Tables 1 and 2). These subjects had the highest and most variable rate of tear

TABLE 1

Rapid initial loss of fluorescein, disappearing completely by 30 minutes in at least one eye of group 1*

Subject No., Age (yrs), Sex	Iris Color	Tear Elimination Coefficient, K_e (%/min) RE	LE
1, 23, M	D	23	19
2, 25, M	D	23	23
3, 21, M	L	22	20
4, 22, M	L	14	14
5, 23, M	L	24	18
6, 28, M	L	33	23
7, 21, F†	D	18	33
8, 26, F†	D	23	14
9, 50, F	D	55	41
10, 19, F†	L	17	14
11, 23, F	L	81	60
12, 24, F	L	28	15
13, 24, F	L	18	17
14, 25, F†	L	14	26
15, 35, F	L	38	33
	Mean	29	25
	S.D.	18	13
	No.	15	15

*D designates dark iris; L, light iris.
†Contact lens wearer.

TABLE 2

STATISTICAL COMPARISONS OF SUBGROUPS OF GROUP 1

Subgroups	No.	Tear Elimination Coefficient K_e (%/min) RE Mean	RE S.D.	LE Mean	LE S.D.
A Males	6	23	6	20	3
B Females	9	32	22	28	16
C Dark irides	5	28	15	26	11
D Light irides	10	29	20	24	14
E Females-no contacts	5	44	25	33	19
F Females-contacts	4	18	4	22	9
		Comparisons			
	df	t	P	t	P
A and B	13	−.98	>.05	−1.32	>.05
C and D	13	−.05	>.05	.28	>.05
E and F	7	2.05	.04	1.12	>.05
RE and LE	14	1.70	.05		

elimination with K_e values in the right eyes of 29 ± 18%/min (mean ± S.D.) and 25 ± 13%/min in the left eyes. No statistically significant differences were observed ($P > .01$) between right and left eyes, males and females, subjects with light and dark irides, or contact lens wearers and nonwearers.

Group 2 consisted of 31 subjects who still had measurable dye in both eyes 30 minutes after application and in whom apparent exponential loss of dye was observed in both eyes between 15 and 30 minutes after application. This group of subjects had the most consistent tear elimination coefficients with the right eyes measuring 11.1 ± 4.7%/min and the left eyes measuring 11.0 ± 4.6%/min. No statistically significant differences were observed ($P > .01$) between right and left eyes, males and females, subjects with light and subjects with dark irides, or contact lens wearers and nonwearers (Tables 3 and 4).

Group 3 consisted of five subjects. These were subjects who showed no apparent loss of fluorescein from the precorneal tear film of at least one eye for a period of 30 minutes after application. All of these eyes, except one, eventually showed the typical decay, but the decay was slower and in some eyes did not begin until 45 minutes after fluorescent tracer was applied to the eye. One eye, the left eye of subject No. 49, showed a steady increase in fluorescence in the precorneal tear film for one hour. The cornea appeared normal and did not stain with fluorescein. The examiner determined, on careful questioning, that this subject had a history of being unable to produce reflex tearing with the left eye (Table 5).

An additional subject was tested on six successive mornings (Table 6 and Fig. 1). The tear elimination coefficient was 7.2 ± 3.8%/min in the right eye and 9.2 ± 3.1%/min in the left eye. The coefficient of variation was 53% in the right eye and 34% in the left eye. The difference in the elimination coefficient between the right and the left eye was not statistically significant ($P > .05$).

Excluding subject No. 49, the mean value of the tear elimination coefficient for all eyes tested was 15.4 ± 11.9%/min. The coefficient of variation between the measured elimination coefficient of the right and left eye pairs of these subjects was calculated according to the following formula:

TABLE 3

APPARENT EXPONENTIAL LOSS OF FLUORESCEIN IN BOTH EYES 15 TO 30 MINUTES AFTER APPLICATION IN GROUP 2

Subject No., Age (yrs), Sex	Iris Color†	Tear Elimination Coefficient, K_e* (%/min) RE	LE
16, 21, M	D	7	16
17, 23, M	D	17	13
18, 26, M	D	9	10
19, 24, M	L	9	4
20, 24, M	L	9	14
21, 27, M	L	11	12
22, 41, M	L	10	13
23, 20, F	D	6	7
24, 21, F‡	D	8	10
25, 23, F	D	16	17
26, 23, F‡	D	14	11
27, 24, F	D	10	13
28, 25, F	D	12	10
29, 43, F	D	23	18
30, 48, F	D	6	9
31, 21, F‡	L	15	10
31, 24, F‡	L	6	6
33, 25, F‡	L	13	17
34, 25, F	L	3	4
35, 26, F‡	L	10	13
36, 26, F	L	11	14
37, 27, F	L	11	6
38, 28, F	L	21	15
39, 30, F‡	L	15	14
40, 30, F‡	L	15	11
41, 35, F	L	8	6
42, 35, F	L	16	19
43, 41, F	L	12	16
44, 43, F	L	10	5
45, 45, F	L	3	3
45, 64, F	L	9	5
	Mean	11.1	11.0
	S.D.	4.7	4.6
	No.	31	31

*Determined from 15 to 30 min segment of fluorescence decay curve.

†D designates dark iris; L, light iris.

‡Contact lens wearer.

$$V_x = 100\% \times \frac{\sqrt{\sum_{i=1}^{n} \left(\frac{(R_i - L_i)}{(R_i + L_i)/2} \right)^2}}{n}$$

where R and L refer to the K_e value of the right and left eye, respectively. The coefficient of variation, determined in this way, was 36%. The frequency distribution of the tear turnover coefficients for the right eye of all subjects was plotted and is shown in Figure 2. The logarithm of the elimination coefficient appears to be normally distributed in this group of subjects (Table 7).

The ages of the subjects ranged from 19 to 64 years; no statistically significant correlation was found between age and tear elimination coefficient. However, most subjects were in the age range from 20 to 30 years, with a median age of 25 years.

DISCUSSION

The mean tear elimination coefficient in these subjects, 15%, is identical to that reported by Mishima and associates[3] and in principle, the techniques are identical. However, the procedure used in this study was intentionally designed for simple implementation in the hands of an ophthalmic assistant. The specific points of simplification are first, that the fluorescein is placed on the tarsal conjunctival surface of the lower eyelid where it is easy to apply without staining the skin of the eyelid, and second, that the fluorophotometer measurements are made in the central 5 mm of the precorneal tear film where alignment of the instrument is simple. The two disadvantages of these simplifications are as follows: (1) it may take longer for the falling portion of the fluorescein decay to occur, as compared to a test where the dye is applied only to the interpalpebral tears, and (2) the method cannot be used with any subjects in whom fluorescein stains the central cornea.

Except for rapid washout of the dye in some subjects, probably caused by reflex tearing, the main source of variation in results might be the rate of exchange of the dye from its depot in the lower cul-de-sac with the precorneal tear film. In some subjects, this exchange may be

TABLE 4

STATISTICAL COMPARISONS OF SUBGROUPS OF GROUP 2

		Tear Elimination Coefficient* K_e (%/min)			
		RE		LE	
Subgroups	No.	Mean	S.D.	Mean	S.D.
G Males	7	10.3	3.2	11.7	3.9
H Females	24	11.4	5.0	10.8	4.8
I Dark irides	11	11.6	5.4	12.2	3.5
J Light irides	20	10.9	4.3	10.4	5.0
K Females-no contacts	16	11.1	5.7	10.4	5.5
L Females-contacts	8	12.0	3.6	11.5	3.3
		COMPARISONS			
	df	t	P	t	P
G and H	29	−.54	>.05	.46	>.05
I and J	29	.44	>.05	1.07	>.05
K and L	22	−.42	>.05	−.50	> .05
RE and LE	30	.19	>.05		

*Determined from 15 to 30 min segments of fluorescence decay curve.

rapid and in some it may be slow. The subjects in Group 3 may represent persons with slow exchange within the total tear pool as well as slower tear elimination. Our data indicate that great variability in test results is not unusual in patients with rapid tear elimination but that much less variability occurs in patients with slow elimination. The frequency distribution of K_e values (Fig. 2) indicates that elimination coefficients less than 1%/min are unusual and probably should

TABLE 5

NO APPARENT LOSS OF FLUORESCEIN BETWEEN 15 AND 30 MINUTES IN AT LEAST ONE EYE OF GROUP 3

		Tear Eliminations Coefficient, K_e‡ (%/min)		Time after which Fluorescence Began to Diminish, (min)	
Subject No., Age (yrs), Sex	Iris Color†	RE	LE	RE	LE
47, 22, F	L	8	6	30	15
48, 24, F*	L	8	7	30	30
49, 24, F	L	7	§	15	§
50, 28, F*	L	8	4	15	30
51, 50, F	L	3	2	45	45
Mean		6.8	4.8		
S.D.		2.2	2.2		
No.		6	5		

*Contact lens wearer.
†L designates light iris.
‡ Determined from falling portion of fluorescence curve.
§ Concentration of fluorescein still increasing in left eye after 60 minutes.

TABLE 6
REPEATED DETERMINATIONS IN A SINGLE SUBJECT

Determination No.	Tear Elimination Coefficient K_e (%/min) RE	LE
1	5	8
2	6	9
3	4	6
4	5	9
5	14	8
6	9	15
Mean	7.2	9.2
S.D.	3.8	3.1

TABLE 7
FREQUENCY DISTRIBUTION OF K_e IN NORMAL SUBJECTS

Percentile	Tear Elimination Coefficient, K_e (%/min)
1	3
2	4
5	5
10	6
20	8
30	9
40	11
50	12
60	14
70	16
80	19
90	25
95	30
98	38
99	45

be considered abnormal. We consider the left eye of subject No. 12 to be abnormal, where the dye concentration increased for longer than an hour, but where no corneal staining was observed. This finding suggests that the rate of loss of fluorescein by diffusion into tissues in contact with the tears is slow and probably relatively slower than loss of water by evaporation. Thus, most of the observed loss of fluorescein must have occurred by flow out of the lacrimal drainage system, a process that requires continuous elaboration of a greater volume of new tears than is lost through evaporation.

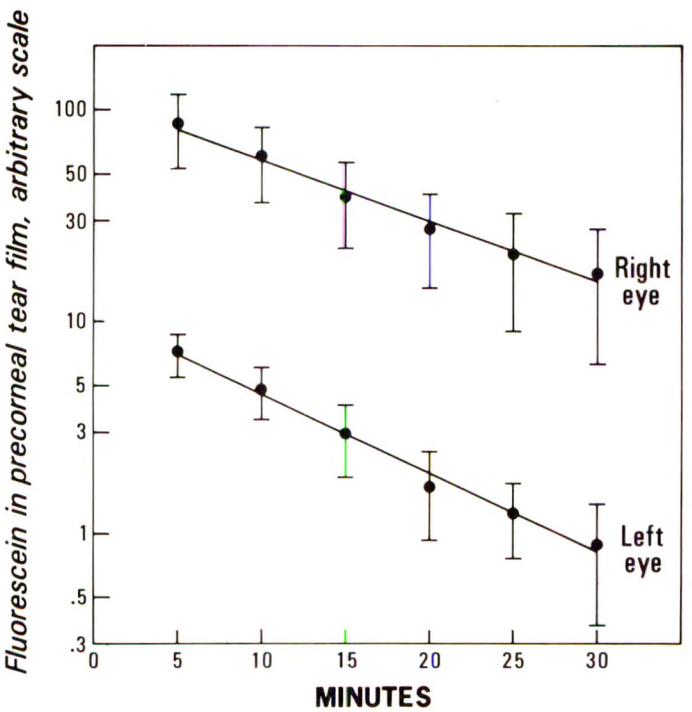

Fig. 1 (Puffer, Neault, and Brubaker). Fluorescence decay, presented in arbitrary units on logarithmic ordinate, versus time. Six determinations in a single subject. Differences in the slopes of the two lines are not statistically significant ($P > .05$).

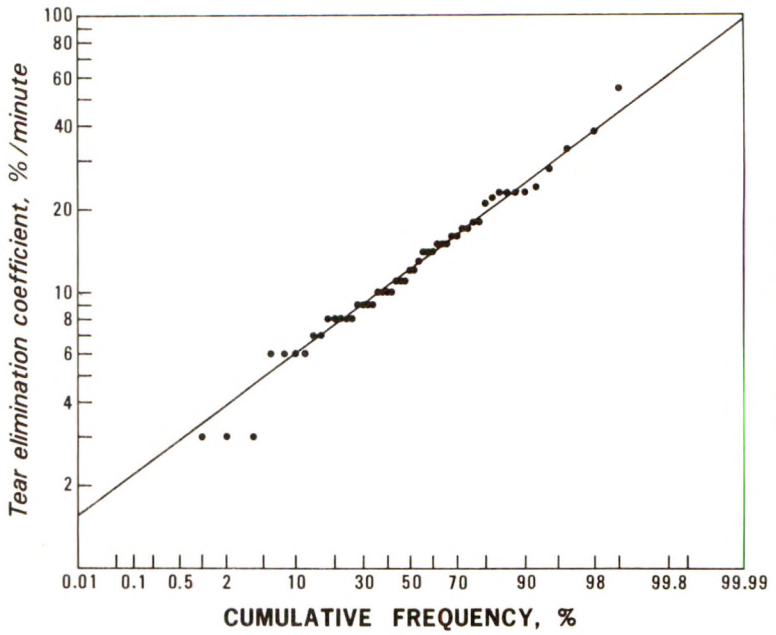

Fig. 2 (Puffer, Neault, and Brubaker). Tear elimination coefficient, presented in percent per minute on logarithmic ordinate, vs cumulative frequency, percent, presented on a Gaussian abscissa. The logarithm of the tear elimination coefficient is linear, indicating a normal distribution.

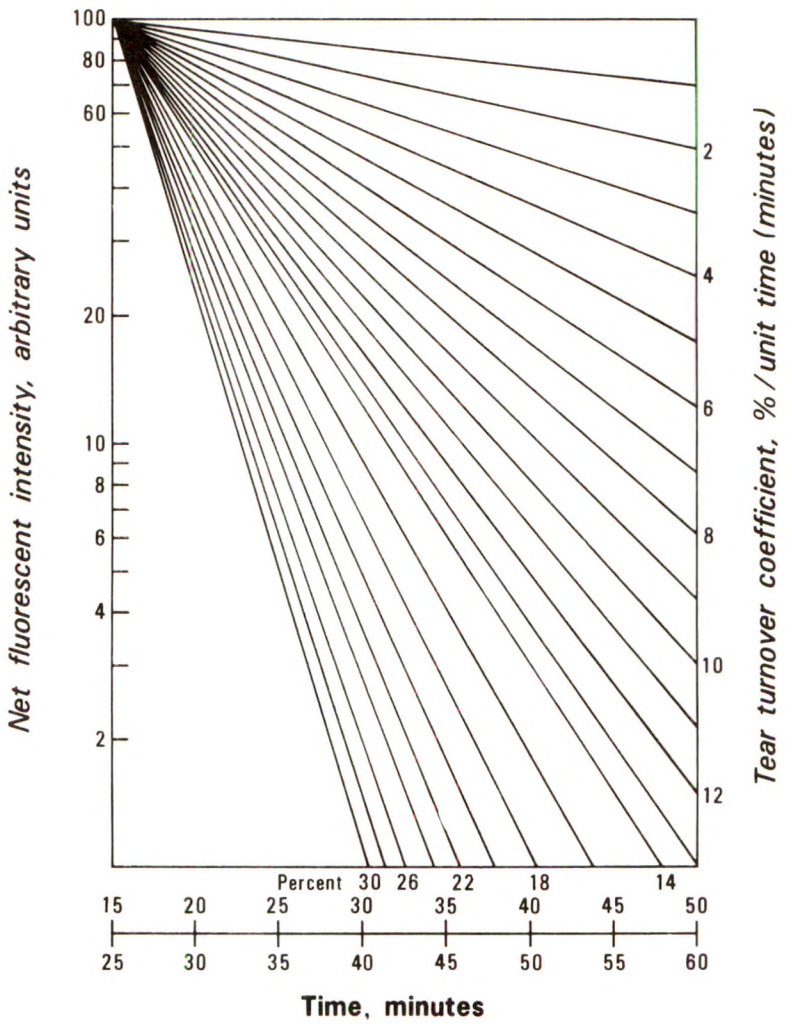

Fig. 3 (Puffer, Neault, and Brubaker). Nomogram for determining the tear turnover coefficient, K_e, in percent per minute. The net fluorescence at some arbitrary starting time (for example, 15 or 25 minutes) after application is assigned the value 100%. Subsequent values of net fluorescence are plotted as a percent of the initial value. K_e is read directly off closest fitting line. Values less than 1%/min are probably abnormal.

These results suggest that a relatively simple clinical test for abnormally low basal tearing could be performed by measuring net fluorescence in the central precorneal tear film, perhaps at 15, 30, 45, and 60 minutes. If the loss of fluorescein, as determined graphically from a semilogarithmic plot of net fluorescence vs time, decreases at a rate of 1 to 2%/min or faster, the test results should probably be considered normal. A nomogram, such as the one shown in Figure 3, could be useful to quantify the results.

Such a procedure is currently being studied to see if patients with clinical signs and symptoms of poor lacrimation show an abnormally low rate of fluorescein loss, as compared to this normal group.

Recently, Lamberts, Foster, and Perry[6] described the results of calibrated Schirmer strip testing in a large number of normal subjects. They found a tear flow of 2.51 ± 1.18 μl/min in unanesthetized eyes and 1.52 ± 1.00 μl/min in anesthetized eyes. If the average tear volume of their subjects was the same as that measured by Mishima and associates,[3] 7 μl, these flow rates would imply a tear turnover coefficient of 36 and 22% for the unanesthetized and the anesthetized eyes. These figures are higher than the 15% average we report here, and suggest that the fluorescein turnover method is less likely to stimulate reflex tearing than the Schirmer test, particularly if no anesthetic is used. The study of Lamberts, Foster, and Perry[6] also showed that 5 to 10% of subjects who have no symptoms have low rates of tear flow, a finding that we also observed. Thus, we conclude that subjects must show extremely low rates of tear turnover before it can be established that their rate of tear production, per se, is abnormal.

Summary

We studied 51 normal subjects with a simple method that permits measurement of the rate of fluorescein loss from the central precorneal tear film. In 15 (29%), no measurable dye remained 30 minutes after application of 1 μl of a 10% solution of sodium fluorescein into the lower cul-de-sac. In 31 (61%) of the subjects, an exponential decay of the dye was observed between 15 and 30 minutes after application. In 5 (10%) of the subjects, a prolonged increase in dye concentration was observed, followed by a steady decrease that began 30 to 45 minutes after application. One eye of one subject had a steady increase in dye concentration for over an hour, and this eye was excluded from the analysis. The mean value for the tear elimination coefficient in all subjects analyzed was 15%/min. The logarithm of the tear elimination coefficient appeared to be normally distributed within the population sample. Analysis of the frequency distribution permitted an estimate that the 95% confidence limits for the tear elimination coefficient, as measured by this method, was 5 to 30%/min. No statistically significant correlations were found between tear elimination coefficient and sex, eye color, or contact lens use.

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PROTEIN AA AND LATTICE CORNEAL DYSTROPHY

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The major component of amyloid deposits associated with plasma-cell neoplasms and with primary amyloidosis is a protein related to the light chain of immunoglobulins.[1–3] However, the major component of amyloid deposits associated with secondary amyloidosis and with familial Mediterranean fever is a protein (protein AA) that is unrelated to immunoglobulins.[1–3] Both primary and secondary amyloid deposits are associated with a structural protein, the P (plasma) component, now known as AP.[4]

The stromal lesions of lattice corneal dystrophy contain amyloid.[5] To the best of our knowledge, the relationship of these amyloid deposits to immunoglobulins or protein AA has not been reported. The present study shows protein AA and protein AP in the amyloid deposits of lattice corneal dystrophy.

CASE REPORT

A 73-year-old woman was referred with the diagnosis of corneal dystrophy. The patient had noted bilateral, painless, progressive loss of vision in both eyes, but greater in the right eye, for about the last 20 years. Symptoms were suggestive of recurrent corneal erosions. The patient had a history of coronary artery disease with a myocardial infarction. She did not have any chronic infectious or inflammatory diseases. Her family history revealed lattice corneal dystrophy. Her father and two first cousins on her father's side were affected.

On examination the patient's visual acuity was R.E.: counting fingers and LE: 6/15 (20/50) with correction. Slit-lamp examination of the corneas revealed a central stromal opacity and stromal, linear, branching opacities that tended to spare the periphery and were characteristic of lattice dystrophy (Fig. 1). The lesions in the right cornea were larger and more numerous than those in the left cornea. Intraocular pressures by pneumotonometry were normal in both eyes. Although the view was obscured by the corneal lesions, the posterior poles in both eyes appeared normal.

The patient underwent a 7.5-mm penetrating keratoplasty of the right eye. No postoperative complications were noted, and the corneal graft has remained transparent with topical corticosteroid therapy.

Fig. 1 (Mondino and associates). Right cornea of patient with central stromal opacity and linear, branching, stromal opacities.

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Material and methods

The host cornea obtained at keratoplasty was bisected, and one half was fixed in 10% formalin and processed for paraffin sectioning with a microtome at 6 μ. The sections were stained with hematoxylin-eosin, PAS, and Congo red.

The other half of the excised host cornea was immediately frozen for sectioning on a cryostat. Sections were cut at 4 μ and mounted on gelatin-coated slides. The sections were fixed in acetone. A few sections were fixed in ethanol and stained with hematoxylin-eosin to confirm the location of fluorescence. By using a direct immunofluorescent technique, fluorescein-conjugated goat antisera to human kappa chains and lambda chains and human IgG, IgA, and IgM were applied to corneal sections at dilutions of 1:5, 1:10, 1:20, and 1:40. After 30 minutes of incubation at room temperature in a dark humid chamber, the sections were thoroughly washed in phosphate-buffered saline (pH 7.4) for 60 minutes. The sections were covered with 90:10, glycerin:distilled water.

Antiserum to protein AA was prepared in the rabbit.[6] This antiserum has been shown to be specific for isolated AA and does not cross-react with amyloid associated with plasma-cell neoplasms or primary amyloidosis.[6] This antiserum has been used to identify protein AA in amyloid deposits associated with familial Mediterranean fever by means of indirect immunofluorescence.[7] Antiserum to amyloid tissue-derived AP was produced in rabbits as previously described.[8] This antiserum has been used to identify protein AP by indirect immunofluorescence.[4] By using an indirect immunofluorescent technique, sections were covered with antiserum to protein AA at dilutions of 1:2 and 1:10 or antiserum to AP at dilutions of 1:4 and 1:10. The sections were incubated for 30 minutes, washed for 30 minutes, and overlaid with fluorescein-conjugated goat antiserum to rabbit IgG at a dilution of 1:20. After 30 minutes of incubation, the slides were washed for 60 minutes. The sections were covered with 90:10, glycerin:distilled water.

As controls for both the direct and indirect immunofluorescent techniques, normal human donor corneas were stained with all the antisera described above. As additional control for the indirect immunofluorescent technique, sections of the patient's cornea were initially incubated with nonspecific rabbit serum instead of rabbit antiserum to protein AA or rabbit antiserum to protein AP before the application of the fluorescein-conjugated goat antiserum to rabbit IgG. To control for autofluorescence, sections of the patient's cornea were prepared without the application of fluorescein conjugates. All of the corneal sections were viewed with a Zeiss fluorescence microscope.

Results

Histopathologic examination of the patient's cornea showed a hyaline pannus between the epithelium and Bowman's layer. The stroma showed eosinophilic deposits that were PAS-positive. These stromal deposits stained positively with Congo red and showed green birefringence with polarized light.

Immunofluorescent examination disclosed no fluorescent staining of the stromal deposits for kappa chains, lambda chains, IgG, IgA, and IgM at dilutions tested. The deposits showed positive fluorescence when rabbit antiserum to protein AA at dilutions of 1:2 or 1:10 followed by fluorescein-conjugated goat antiserum to rabbit IgG at 1:20 was applied to the corneal sections (Fig. 2). This fluorescence was eliminated when nonspecific rabbit serum instead of antiserum to protein AA was applied before the fluorescein-conjugated antiserum to rabbit IgG. The deposits also showed posi-

Fig. 2 (Mondino and associates). Section of right cornea showing fluorescence of stromal deposits with application of rabbit antiserum to protein AA followed by fluorescein-conjugated goat antiserum to rabbit IgG.

tive fluorescence when rabbit antiserum to protein AP at dilutions of 1:4 or 1:10 followed by fluorescein-conjugated goat antiserum to rabbit IgG at 1:20 was applied to the corneal sections. When nonspecific rabbit serum instead of antiserum to protein AP was applied before the fluorescein-conjuated antiserum to rabbit IgG, this fluorescence was eliminated. A comparison with corneal sections stained with hematoxylin-eosin showed that these brightly fluorescent areas were localized precisely to the sites of the amyloid deposits. A comparison with sections of the patient's cornea prepared without the application of fluorescein conjugates eliminated the possibility that autofluorescence was being read. Normal donor corneas did not show these brightly fluorescent deposits.

Discussion

The major component of amyloid deposits associated with primary amyloidosis or plasma-cell neoplasms is a protein related to the light chain of immunoglobulins.[1–3] These amyloid deposits consist of whole light chains or fragments thereof with molecular weights ranging from 7,500 to 23,000 daltons. Biochemical studies suggest that usually the variable region of the light chain is present and at times the variable and constant regions. Both kappa and lambda light chains have been found. Most of these patients have an M-component in their serum or urine related or identical in structure to that in the tissue.[1,2] The pathogenesis of the M-component deposition as amyloid in tissues is uncertain.

The major component of secondary amyloidosis and amyloidosis associated with familial Mediterranean fever is designated protein AA. It has a molecular weight of about 8,500 daltons and an amino acid sequence having no likeness to any immunoglobulin.[1–3] The finding of a larger antigenically related protein (SAA) in normal serum and increased amounts in the serum of patients with amyloidosis and other chronic diseases may indicate that this represents the precursor protein possibly attached to a transport protein.[1–3]

Our study showed protein AA and protein AP in the stromal deposits of lattice corneal dystrophy. Fluorescent staining of the stromal deposits for kappa chains, lambda chains, IgG, IgA, and IgM could not be shown. Thus, not only secondary amyloid and the amyloid of familial Mediterranean fever but also the amyloid of lattice corneal dystrophy appear to be related to amyloid protein AA.

SUMMARY

A 73-year-old woman underwent corneal transplantation because of lattice dystrophy. Histopathologic examination of the excised host cornea disclosed eosinophilic deposits that stained positively with Congo red and showed green birefringence with polarized light. Immunofluorescent examination showed protein AA and protein AP in the stromal deposits. To the best of our knowledge, this is the first report of protein AA and protein AP in the amyloid deposits of lattice corneal dystrophy.

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EPITHELIAL RESPONSE IN PENETRATING KERATOPLASTY

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Although recognized as the primary source of donor antigenicity, the epithelium of a donor cornea is not usually a source of clinical problems.[1] In animal models donor epithelial cells have been shown to survive for several months,[2] but this has not been shown conclusively in humans. Classic epithelial rejection is uncommon but its occurrence may indicate persistence of donor epithelial cells for long periods.[2,3] Corneal epithelial microcysts develop in a variety of corneal conditions either secondary to corneal disease, such as herpes simplex keratitis,[4] or as a primary dystrophy.[5] Tripathi and Bron[6,7] suggested that their development represents a nonspecific reaction to a variety of unrelated conditions, based on the limited number of reaction patterns epithelial cells can respond with.

Development of discrete white dots (presumed microepithelial cysts) in the donor corneal epithelium central to the wound edge occurred in many patients undergoing routine keratoplasty. I studied the development of these epithelial dots and their histology in a prospective group of 30 patients and confirmed that donor epithelial cells persist for long periods of time after human keratoplasty. The observed change in dot distribution may indicate that lateral cell movement occurs in an intact corneal epithelium.

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SUBJECTS AND METHODS

Thirty consecutive patients undergoing penetrating keratoplasty for a variety of causes were followed up for 15 months by monitoring standard corneal factors including specular microscopy, pachymetry, keratometry, refraction, and slit-lamp photography.

Donor corneas were stored in McCarey-Kaufman media from one to three days, except two corneas used after moist chamber preservation. The surgical procedure was similar in all cases, the donor cornea being punched trephined from the endothelial side, either the same size (isometric) or disparately larger by 0.5 or 0.2 mm than the recipient bed. The recipient bed was manually trephined, using a trephine with inner and outer 360-degree view of the cutting edge. Anterior segment stabilization was provided by a single or double Flieringa ring and vitrectomy, coreoplasty, lensectomy, and angle restoration was performed as necessary. The donor button was secured by using single or double continuous 22 μ or 16 to 18 μ nylon, and 22 μ Prolene in one case. Operative keratometry was performed on all cases at the end of the procedure to achieve spherical or a slightly steeper radius of curvature at 90 degrees with suture adjustment or interrupted suture placement. Triamcinolone acetonide (Kenalog) and gentamicin sulfate (Garamycin) were administered topically and subconjunctivally at separate sites. With extensive vitrectomy or repeat transplants, systemic corticosteroids (100 mg of prednisone) were administered orally.

At the end of the procedure a depressed area of donor cornea was present central

TABLE 1

APHAKIC RECIPIENT BED DISEASE

Disease	No.	Disparate No.
Bullous keratopathy	7	7
Fuchs' dystrophy	3	3
Trauma	3	3
Keratitis	1	1
Congenital dystrophy	1	1
Total	15	15

TABLE 2

PHAKIC RECIPIENT BED DISEASE

Disease	No.	Disparate No.
Keratoconus	5	1
Congenital dystrophy	5	1
Fuchs' dystrophy	3	2
Herpetic keratopathy	1	1
Graft rejection	1	0
Total	15	5

to the incision, which produced a slight doughnutlike effect. It was in this area that the early observations were made. Dot numbers were counted by observation and where possible by photography. Three areas were defined on the donor cornea in the form of a grid consisting of an outer diameter of 1.5 mm, midzonal of 3 mm, and an inner diameter of 4 mm. Dots were counted by observation on at least three occasions before suture removal, and during the second through fourth week follow-up visits after suture removal. The limitations of direct counting were recognized, but suitable photographs were not possible in most cases because many pupils would not dilate to greater than the size of the keratoplasty, making retroillumination photographs difficult. No dots developed in the nonoperated opposite control eye. Histology of these epithelial dots was obtained in six cases. The epithelium was peeled off or scraped for 2 to 3 mm by using a forceps and blade. Collodion was not used for fear of damaging the transplant. The specimens were fixed in formaldehyde and histologically processed.

RESULTS

Of the 30 patients undergoing penetrating keratoplasty, 15 were aphakic, requiring some form of vitrectomy, coreoplasty, angle restoration, or lens extraction. Fifteen patients were phakic. The type of disease of the recipient cornea for the aphakic and phakic groups is shown in Tables 1 and 2. The onset and incidence of corneal dots is described in Table 3; 47% developed epithelial dots with a mean initial onset at 6.5 weeks and the mean graying time of 11 weeks.

The average dot number counted during the sixth month was 697 in the peripheral zone and zero in the others (Table 4). The average peripheral dot density per suture interval was 30 with a range from 0 to 55. The dots confined them-

TABLE 3

ONSET AND INCIDENCE OF EPITHELIAL DOTS

	No.	Donor Involvement	Percent Affected	Mean Initial Onset (wks)	Mean Graying (wks)
Isometric	10	3	30	7	12
Disparate	20	11	55	6	10
Total	30	14	47	6.5	11

TABLE 4

EPITHELIAL DOT DISTRIBUTION

Average Nos.	Presuture Removal		Postsuture Removal
	6 mos	10-14 days	(20-30 days)
Peripheral (1.5-mm diameter)	697	22	3
Midzonal (3-mm diameter)	0	230	3
Central (4-mm diameter)	0	5	36

selves to a diameter of 1.5 mm central to the sutures (Fig. 1). After suture removal, the density of the dot distribution changed rapidly with the average number being highest in the midzonal area at ten to 14 days after suture removal, and highest in the central zone at 20 to 30 days after suture removal.

There was no statistical difference in incidence of dot formation between the disparate and isometric groups ($\chi^2 = 1.68$ with one degree of freedom). One patient developed a few epithelial dots in the recipient bed of the cornea. The degree of donor disparateness included one case 1 mm larger; 15 cases were 0.5 mm and four cases 0.2 mm larger. Pigmentation of the overlying donor epithelium above these dots was seen in two cases. An attempt to correlate dot density with the steepest and flattest astigmatic meridian showed no trend in 15 cases and was not pursued. Drug therapy such as topical corticosteroids did not alter the development of these dots. Reformation of these dots occurred after removal of peripheral donor epithelium for histology, but only if the nylon sutures were still present.

Histology of these epithelial dots was obtained in six cases. Only two of the six specimens were of cytologic value (Figs. 2 and 3). These were examined by light microscopy with standard stains. The epithelial layer was normal in the number, size, and distribution of the basal, intermediate, and superficial cells. The cytoplasm of a few of the basal cells was paler than normal but mitosis was rare. No sex chromatin bodies were identified.[8] (The donors were of opposite sex to the recipients.) Lying in the intermediate layer

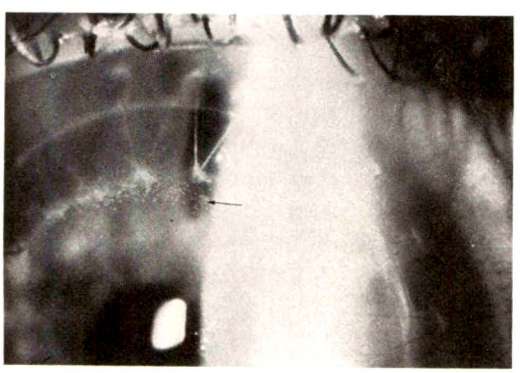

Fig. 1 (Kaye). Epithelial dots (arrow) lying between and central to nylon sutures in donor cornea at 11 weeks. Glassy material lies along suture tracks (×16).

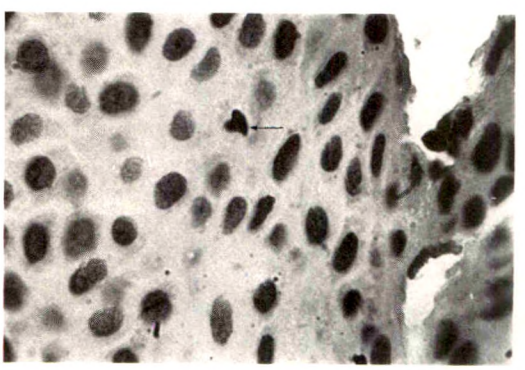

Fig. 2 (Kaye). Histologic section of epithelium postoperatively from donor cornea. Normal epithelium, pale basal cells, damaged epithelial cells with pyknotic nuclei (arrow). Normal surface cells (hematoxylin and eosin, ×100).

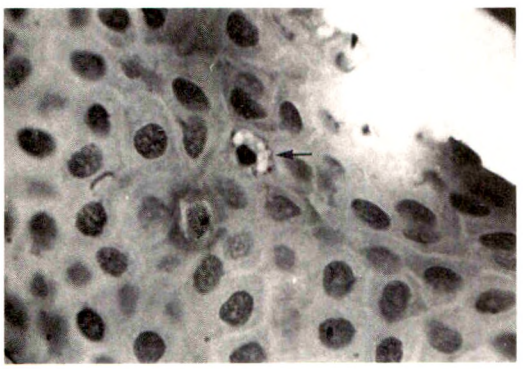

Fig. 3 (Kaye). Histologic section of donor epithelium. Presumed intercellular cysts (arrow) (PAS, ×100).

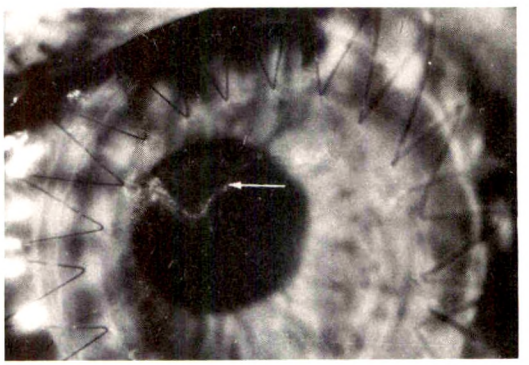

Fig. 4 (Kaye). Donor epithelial rejection at two months. A line of degenerating epithelial cells (arrow) with normal endothelium (×10).

were individual cells in various stages of degeneration. Most cells contained dark pyknotic nuclei and lightly staining cytoplasm and the cells appeared swollen. In others the cytoplasm was vacuolated. Usually three or four of these cells per high-power field could be identified. No free nuclei were noted and although none of these cells was present in the superficial layer, possibly they had lost their nuclei and consisted of collapsed cytoskeletons wedged between these cells. These cells seemed to correspond in size to the dots identified clinically (about 10 to 20 μ in size). Coalescence of these cells was noted in a few areas forming intercellular microcysts. Fragments of normal basement membranes were found in most sections.

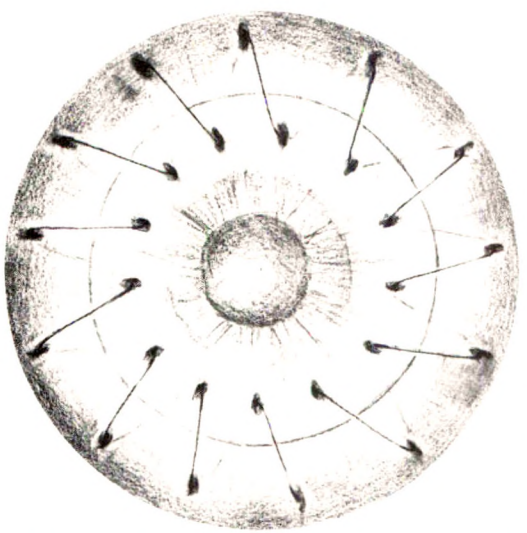

Fig. 5 (Kaye). A drawing one week postoperatively showing compression and swollen donor cornea producing an angulated and doughnut-ring effect centrally.

Finally, seven patients developed endothelial graft rejection and one patient developed a typical epithelial rejection (Fig. 4) unassociated with any endothelial disease. Histology in this case showed the presence of epithelial cells and remnants of epithelial cells together with a few white blood cells.

The general development of these epithelial dots (Fig. 5) included the following: Approximately six weeks after surgery a series of fine clear glasslike dots appeared (dissimilar from the subepithelial fluid pockets seen around the sutures) in a 1- to 2-mm region central to the sutures in the donor cornea. The fine dots lay primarily in the depressed zone central to the swollen donor cornea edge and occasionally in the recipient bed, again peripheral to the suture (Fig. 6). During the next eight to 12 weeks the dots changed in color to a gray-white usually irregular ovals approximately 10 to 20 μ

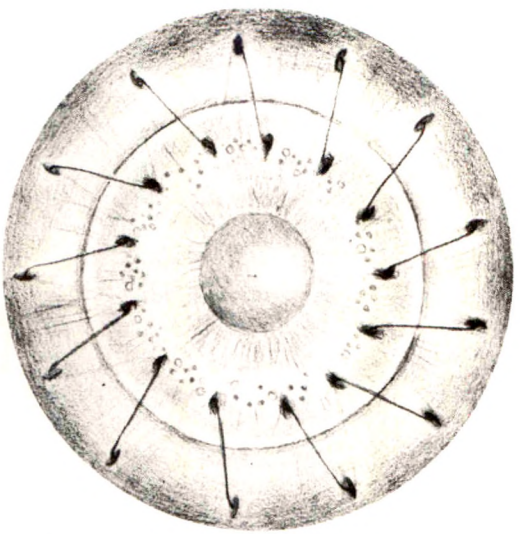

Fig. 6 (Kaye). The development of fine glasslike dots between sutures at six weeks, lying in an angulated area of the cornea.

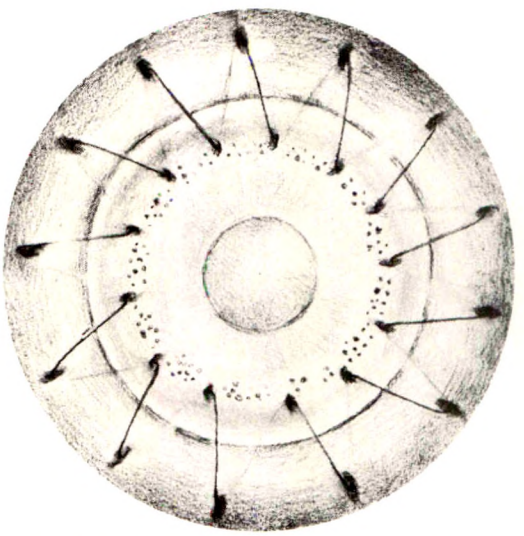

Fig. 7 (Kaye). Clear dots have changed in color to a slate gray by 12 weeks. Variable quadrant density of dots, with a fine circular epithelial pigment line noted.

in size (using the 22 μ nylon suture as a standard marker [Fig. 7]). Some quadrants had less dense accumulations of these dots. The dots did not coalesce and numbered approximately 20 to 40 between each suture. Toward the 20th week a fine epithelial pigment line could be observed. Within 72 hours after the epithelium had covered the defects created by removing the sutures, the number of dots decreased in the peripheral donor cornea (Fig. 8). The decrease was partly caused by the presumed centripetal movement of these dots, and loss caused by the normal vertical movement of these cells (Fig. 9). All dots were absent by 30 days. At no stage were these associated with erosions or fluorescein staining, and the dots were clearly distinguishable from wound scars.

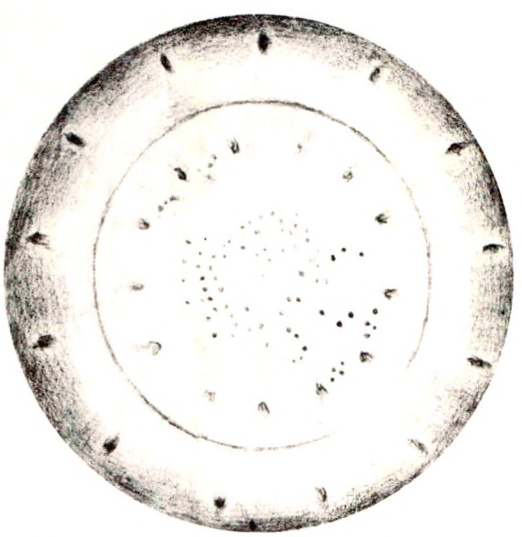

Fig. 8 (Kaye). After the removal of the sutures the dots decrease in numbers partly because of their centripetal movement.

Discussion

Formation of epithelial dots in donor corneas away from the wound edge, and apparently related to an area of tissue angulation, may be a nonspecific response of the epithelium. Corneal epithelial cells can respond to stress in a limited number of ways. They may produce excessive basement membrane,[9] altered basement membrane,[10] cell mitosis and transformation,[11] intraepithelial micro-

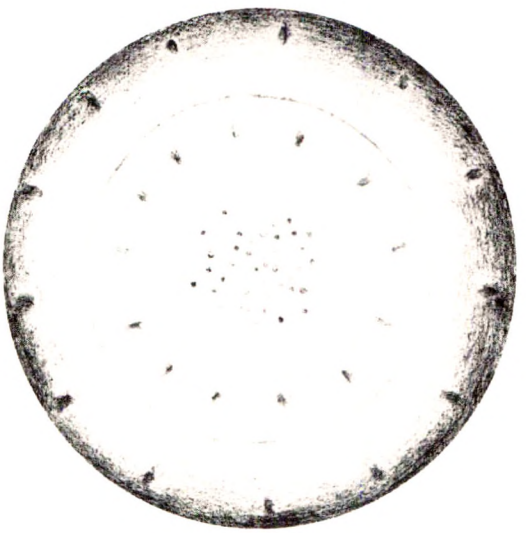

Fig. 9 (Kaye). Central remnants of dots with none in periphery.

cysts,[12] and intracellular alterations as in Meesman's dystrophy.[13]

The morphogenesis of these epithelial lesions was not revealed in this study. In 1949, Weiss[14,15] showed that the shape of a cell can be altered by distorting the matrix it lies in. Subsequently, he coined the term "contact guidance" to describe the method of controlling the pattern of cell growth in cultures by varying the contour of the contact surface. Behavior of the corneal epithelial cells may be a function of stromal compression, thus explaining the circular orientation, but not the relatively fixed position of these abnormal cells in the epithelium for long periods of time. Normal vertical movement of epithelial cells, in the presence of so many cellular microcysts, should have provided some surface pitting and clinical evidence of staining with fluorescein unless these cells consisted of collapsed cytoskeletons wedged between superficial cells. This feature was absent histologically. The presence of stress-induced grooves on the stromal surface could not be evaluated by this method as the epithelium was separated from the stromal base.

The relationship of this epithelial response to the sutures appeared inconsequential at first. However, assuming that the dots migrated centrally after the sutures had been removed, recurred only if the sutures were present, and have not been noted with silk sutures, a special relationship exists with nylon and Prolene sutures. Additionally, the development of the midzonal and central dots has not been observed after suture removal in cases where the initial peripheral zone did not develop, which excludes the possibility that these dots occur spontaneously in these areas.

Sex chromatin analysis in two cases of male to female transplants confirmed that minimal recipient to donor epithelial cell replacement occurred over a six-month period. This may indicate persistence of the donor epithelium for long periods of time as described by Khodadoust and Silverstein.[2]

The question of whether centripetal movement of epithelial cells is normal in the presence of a fully intact epithelial layer has not been answered.[16–20] Others[16,17,19] studied the vertical movement of epithelial cells using tritiated thymidine in rats. These workers confirmed that vertical cell turnover occurred within seven days, but were not able to show lateral cell movement. Murphy and associates[21] have shown that corneal epithelial cells will spread to cover bare corneal stroma, but this is a different question from that occurring in an intact cell layer. However, their work indicated the importance of recognizing the origin of corneal epithelium, either being conjunctivally or corneally derived. They showed that conjunctivally derived corneal epithelium has the ability to transform back into typical conjunctival epithelium, and this is associated with an obligatory vascular response.[22] This raises the question of whether the corneal epithelium normally replaces its own

cells or draws upon the conjunctiva. If lateral cell movement is a normal occurrence, then under certain stress conditions the conjunctiva may supply epithelium and vessels to the cornea. Examples would include long-term contact lens wear and peripheral inflammations, such as vernal catarrh. The present study showed that a change in corneal epithelial dot distribution does occur in a centripetal fashion and is evidence for lateral corneal epithelial cell movement.

Improved observing and counting techniques, safe cell tagging techniques, and the relationship to the sutures are now under investigation.

Summary

In 30 patients who were followed up, discrete corneal epithelial dots developed in a strictly confined area of the peripheral donor cornea within two months after penetrating keratoplasty. The incidence was higher, although not statistically significant, in the disparate group (55%) as compared to the isometric group (30%). The change in dot density that occurs after nylon suture removal is consistent with the idea of lateral cell movement in the corneal epithelium. This study confirms that donor epithelium persists for long periods of time.

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Gary Fletcher and Kurt Stenn, M.D., assisted with the pathology.

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ENDOGENOUS *CANDIDA* ENDOPHTHALMITIS IN INFANTS

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All of the more than 100 reported cases of endogenous (hematogenous) *Candida* endophthalmitis have occurred in adults or in children at least 6 years old, except for a group of ten infants who were younger than age 11 months at the time they acquired the infection.[1–9] Five of these ten infants acquired their infection in the newborn period.[4–7,9] Although the general subject of endogenous *Candida* endophthalmitis has been reviewed,[10] relatively little attention has been given to the specific study of this entity in infants.[6–9]

I describe herein two additional cases of the occurrence and resolution of endogenous *Candida* endophthalmitis in newborn infants, and highlight findings in one of the patients: free-floating vitreous opacities ("ballon vitréen").[1,11] The second patient's lesions resolved in a more conventional manner, although her course was further complicated by retinopathy of prematurity.

CASE REPORTS

Case 1—A 3,910-g male infant was born in October 1974 after 42 weeks' gestation. Although the pregnancy and labor had been uncomplicated, the infant failed to breathe spontaneously and required resuscitation. On physical examination there was a unilateral partially cleft lip, with intact palate. The abdomen was markedly distended. Bowel obstruction was diagnosed and, at age 2 days, exploratory laparotomy revealed midgut volvulus and small bowel necrosis. A partial small bowel resection was performed and a total parenteral alimentation catheter was inserted into the external jugular vein. Postoperatively, the patient was given penicillin intravenously and kanamycin intramuscularly.

At age 8 days, a moderate fever, mottling of the skin, and a papular rash developed. Urinalysis showed mycelia, and cultures subsequently grew an unspecified *Candida*. Blood culture that day also grew a *Candida* species, later identified as *C. tropicalis*. The intravenous catheter was removed.

Three days after the onset of fever, the antibiotics were changed to ampicillin and gentamicin, which were administered for three more days and then discontinued. The infant appeared to be doing generally better, and a definite diagnosis of *Candida* sepsis was not yet made, although serial blood cultures were begun. At age 17 days, yeast was found on microscopic urinalysis. By the following day, additional blood cultures were growing *Candida*, and the infant was given intravenous infusions of amphotericin B at a dosage of 0.50 mg/day, which was increased over a four-day period to 4 mg/day. After two days of treatment, the infant seemed more active. On the fifth day of antifungal therapy (age 23 days), jaundice and hepatomegaly were noted; although the cause was still obscure, *Candida* hepatitis was suspected. The infant was also becoming less active, and because in vitro studies had shown his *Candida* to be sensitive to flucytosine, this drug was added at a dosage of 50 mg/kg of body weight per day. Generalized edema was developing and the serum potassium level was in the lower range of normal. Because nephrotoxicity caused by amphotericin B was thought to be responsible, that drug was withheld for two days and then resumed on an alternate-day basis. On the 14th day of amphotericin B, and the ninth day of flucytosine treatment (age 32 days), all medication was discontinued. All subsequent blood cultures were negative.

On examination at age 36 days, the eyes were externally normal, except for moderate scleral icterus. The pupils were round and reacted to light normally. Portable slit-lamp examination showed no anterior segment anomalies or inflammation. A persistent pupillary vessel system was noted inferotemporally in the left eye. Through binocular indirect ophthalmoscopy, the vitreous of both eyes contained numerous fluffy cotton-ball-like lesions, varying in diameter from about 1 to 2 mm, that appeared

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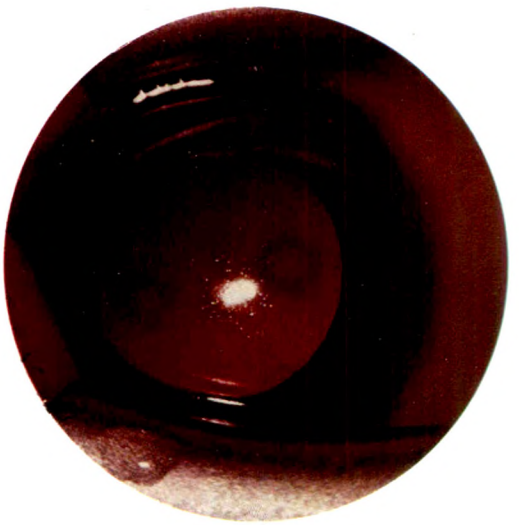
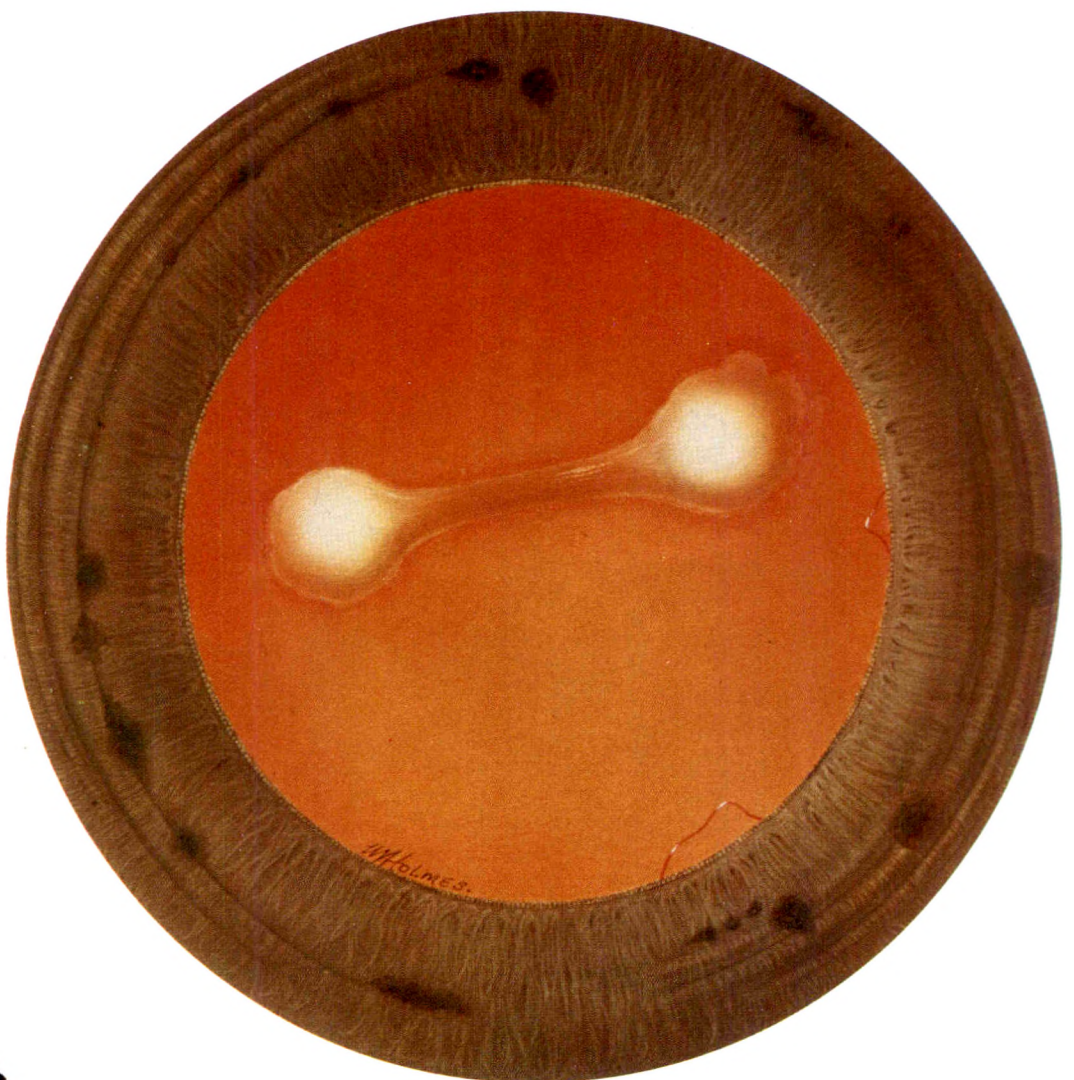


Fig. 2 (Palmer). Case 1. External view, left eye. The two migrant spherical vitreous floaters are easily seen suspended immediately posterior to the lens. Right, The bright spot between the two lesions is a corneal light reflection. Bottom, Artist's conception, based on several photographic views. A refractile connecting strand of vitreous has been emphasized. At the iris border (2:30 and 5 o'clock) are remnant pupillary membrane vessel loops.



to be suspended just anterior to the retina and quivered upon saccadic eye movements. These spherules were located mainly in the middle and far periphery, although a few were seen more posteriorly in the left eye (Fig. 1). Most of the vitreous lesions were discrete, but there was some confluence in a few areas of the far periphery in both eyes. The vitreous in general was clear, except for a slight localized haze surrounding each of the fluffy preretinal lesions. In the left eye, there was one splinter hemorrhage near the disk, and a single white intraretinal lesion resembling a colloid body was present 1 1/2-disk diameters inferotemporally from the fovea. The latter lesion did not change during one month of observation.

Frequent ophthalmoscopy was performed to see if changes in the vitreous opacities could serve as an indicator of whether the *Candida* organisms had been eradicated by the antifungal treatment. Despite the discovery of intraocular lesions after the termination of therapy, antifungal therapy was not resumed because of the evidence of possible drug toxicity. Daily ocular examinations revealed no definite changes in the intraocular lesions until ten days after antifungal therapy had been stopped. At that time, the vitreous opacities seemed better defined, suggesting that they were shrinking or that the surrounding vitreous haze was diminishing, or both. Over the ensuing days, interconnecting strands were evident among some of the lesions that previously seemed to be discrete. Retinal pigment aggregation developed, underlying some of the more peripheral lesions in the left eye.

Three weeks after the diagnosis of endogenous *Candida* endophthalmitis, a remarkable change occurred in two of the more posteriorly situated preretinal opacities in the left eye. These discrete spheroidal floaters rested temporal to the macula and appeared to be connected to the retina or internal limiting membrane by thin strands through the vitreous. Over a three-day period, they broke free, moved anteriorly and slightly temporally, and came to rest immediately behind the lens. They became easily visible, even on flashlight examination, as spherical, gray-white, fluffy opacities lying in the vitreous just behind the posterior lens capsule (Fig. 2). Their new position made a view of the retina more difficult. During this same period of time, that is, age 7 weeks, vitreous bands connecting some of the more peripheral, previously discrete lesions were becoming even more evident. Several of these bands appeared adherent to the retina. Retinal pigmentary disturbance was evident surrounding their retinal terminations (Fig. 3).

The two retrolental spherules in the left eye did not perceptibly diminish in size or change position during two weeks of observation, and at age 9 weeks the infant was discharged for outpatient care. Three months later, the infant was admitted to the hospital because of failure to thrive, and the diagnosis of cystic fibrosis of the pancreas was first made. The jaundice had disappeared. The eyes were almost normal, except for some far peripheral wavy vitreous strands, and they showed no signs of retinal traction. Only wispish remnants of the retrolental spherules were visible by ophthalmoscopy and slit-lamp examination, 4 1/2 months after cessation of antifungal therapy.

Case 2—A 920-g female infant was born 14 weeks prematurely to a multiparous mother in March 1975. There was a history of spontaneous rupture of the amniotic membranes three days previously, and the mother had become febrile and amnionitis was diagnosed. The infant was somewhat sluggish at

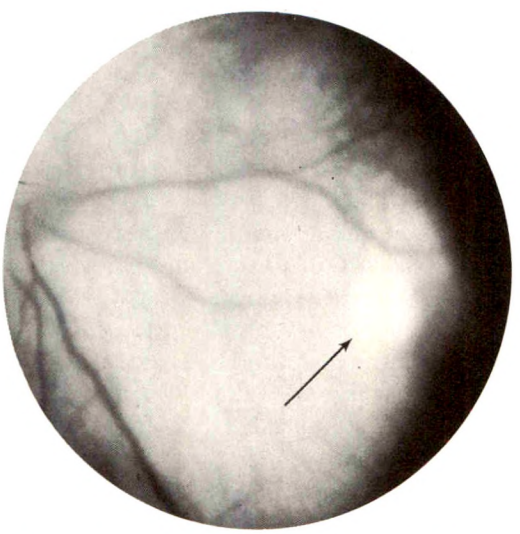


Fig. 1 (Palmer). Case 1. Typical preretinal lesion (arrow) with spherical vitreous opacity anchored to retina, inferotemporal from disk, left eye. The optic disk is seen at the upper left edge of the photograph.

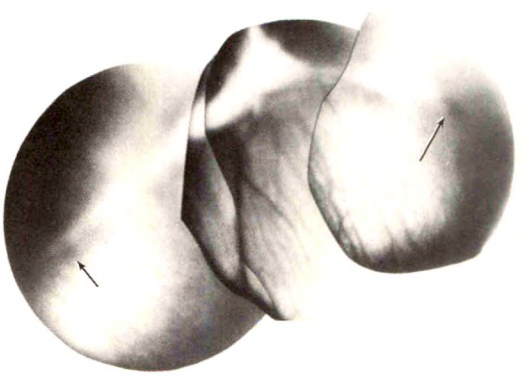


Fig. 3 (Palmer). Case 1. Left eye, Periphery at 11 o'clock. Vitreous bands that developed as the posterior lesions resolved. At the extreme tips of the branching white band (arrows), aggregation of retinal pigment where the band is anchored to the retina or lamina vitrea is barely discernable.

birth and, on general physical examination, was described as "foul-smelling," but seemed otherwise normal for gestational age. Culture specimens were obtained from multiple sites, and she was given ampicillin and gentamicin intravenously on the first day. During the first two weeks of life the infant required treatment for hypocalcemia, hyperglycemia, and hyperbilirubinemia. Although these responded to treatment, the infant also had recurrent apneic spells, which were treated with oxygen, and at age 7 days continuous respirator therapy became necessary.

On that day, the infant was screened for retinal oxygen toxicity, and no abnormalities were found. At age 19 days, a blood culture was drawn that subsequently grew an unspecified *Candida*. The same day a heart murmur of patent ductus arteriosus was heard. All blood cultures before this date had been negative, and blood cultures repeated four and eight days later were again negative. At age 20 days, chronic digoxin therapy was started, the infant was given a blood transfusion, and the antibiotics were discontinued. At age 24 days, budding yeast was found in the urine, and a culture later yielded unspecified *Candida*. The next day surgical ligation of the patent ductus arteriosus was performed. On the day of operation, a urine culture was done that later was positive for *Candida*. Postoperatively, despite transient pulmonary atelectasis, the infant recovered. Two days postoperatively, cultures of blood, urine, and spinal fluid were planted and the infant was again given a course of ampicillin and gentamicin. The cultures were all negative. Six days postoperatively, all antibiotics were stopped, because the only possibly invasive microorganism that had been cultured was *Candida*. The infant began receiving a one-month course of nystatin orally.

On the seventh postoperative day, at age 32 days, lesions considered typical for *Candida* retinitis were found. The posterior retina of each eye showed one round, slightly raised, light gray opacity about 1/4 disk diameter in size. In the right eye, this was in the superotemporal quadrant, and in the left eye, it was just peripheral to the inferotemporal edge of the macular area. The left retinal lesion differed from that in the right eye in that it was surrounded by fine, satellite lesions also involving the inner retinal layers. The infant began receiving 1 mg daily of amphotericin B infused over a two-hour period. A skin rash had developed, but resolved by age 36 days, and yeast was no longer present in the urine.

At age 42 days, a second intraocular lesion was observed in the left eye, located 2 1/2 disk diameters nasal to the disk, and identical in appearance to the pre-existing isolated lesion in the right eye. However, because the right lesion was simutaneously beginning to flatten out and shrink, the drug therapy was tentatively thought to have been effective. By the tenth day of intravenous amphotericin B treatment, it had become impossible to maintain percutaneous infusion because of obliteration of the infant's larger subcutaneous veins. The amphotericin B was discontinued and the ocular lesions were monitored.

At age 49 days, although the right eye lesion was continuing to flatten, those in the left eye had become spherical and had risen slightly off the retina into the vitreous. On that same day, definite retinal neovascular changes of oxygen toxicity were appearing in the temporal periphery of both eyes, associated with characteristic retinal vascular dilatation in the posterior pole. By age 57 days, the right eye *Candida* lesion had essentially resolved, leaving only a focal retinal pigment disturbance, whereas the left eye lesions remained unchanged. The bilateral peripheral retinopathy of prematurity was developing an apparent mesenchymal shunt.[12]

At age 70 days, the paramacular lesion in the left eye had disappeared, leaving only subtle local irregularity of the light reflections from the internal limiting membrane. No visible retinal pigment disturbance in the left eye was evident. The persistent spherical preretinal vitreous floater nasal to the disk in the left eye had gradually decreased to half its size at discovery, and was now only about one eighth disk diameter. It remained immediately anterior to the retina, suspended in the vitreous, until the patient was lost to follow-up after discharge from the hospital.

Discussion

Edwards and associates[10] and Robertson, Riley, and Herman[13] have discussed the clinical factors that predispose patients to the development of candidemia and endogenous *Candida* endophthalmitis. Newborn infants are probably at higher risk for the development of endogenous *Candida* endophthalmitis, because of the normally deficient host defense system of newborns[14] and reduced killing ability of leukocytes for *Candida* in infants.[15] Ferry[6] pointed out that affected older children differed from adults, in that they had no history of any antecedent abdominal surgery; yet the presence of this history in Case 1 and three other infants[3–5] clearly suggests that this association may be as significant in infants as it is in adults. All five previously reported neonates who developed endogenous *Candida* endophthalmitis[4–7,9] were of premature birth weight, as was the infant in Case 2. Case 1, to the best of my knowledge, is the first full-term birth weight infant to be described with this condition.

Vitreous floaters have been described in endogenous *Candida* endophthalmi-

tis,[1,2,11,13,16] but the potential for their migration has not been emphasized. In one report, the origin of the floater was described[1]; the lesion became elevated and finally separated from the retina to rise into the vitreous. The evolution of the lesions in Case 1 was particularly similar, and they were observed to hover, sway, and quiver with shifts in the surrounding medium, before breaking loose, then assuming a more spherical, and less elongated or drop-like shape (Fig. 4). The unusual forward migration of the spherules apparently took place through the main body of the vitreous (secondary vitreous), rather than along Cloquet's canal, although the route of movement was not directly observed. An alternative interpretation would be that previously undetected ciliary body lesions shifted into the pupillary axis, as the posterior lesions shifted into the far periphery and out of view. This interpretation seems unlikely in view of Edwards and associates'[17] observation of the rarity of ciliary lesions in this disease. Case 2 was carefully studied specifically for migration of the vitreous floaters, but no migration was detected. The lesions in the second case were smaller, but other factors could also account for their apparently different course; for example, the timing of therapy, the particular species of *Candida* involved,[18,19] or possibly even interhost differences in resistance to infection.[19] In Case 1, the anterior vitreous spherules dissipated over a period of months.

In rabbits with experimental endogenous *Candida* endophthalmitis, preretinal spheroidal opacities were observed by Hoffman and Waubke.[20] These have also been studied by Edwards and associates,[17] who noted that the course of these lesions is compatible with that sometimes

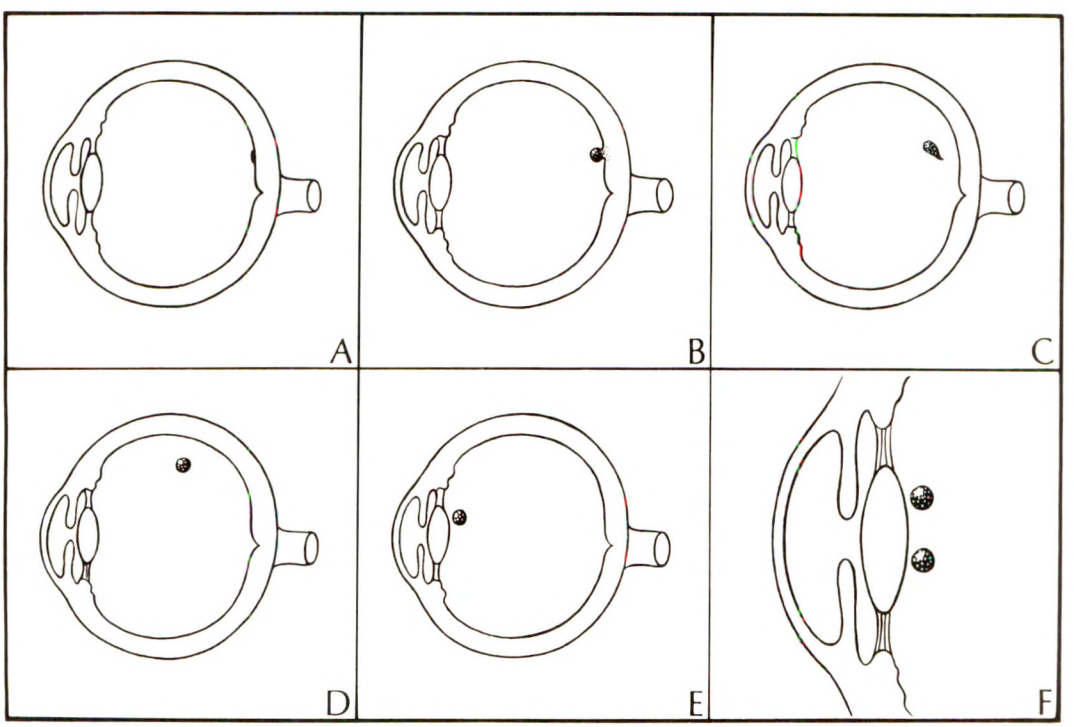


Fig. 4 (Palmer). Evolution of vitreous floaters in endogenous *Candida* endophthalmitis. (A) Chorioretinal lesion; (B) lesion becomes more elevated; (C) lesion separates from retina; (D and E) forward migration (exact route speculative); (F) floaters become visible in retrolental space.

described in humans; that is, many will gradually resolve, sometimes even without any therapy.[21] However, the infection can destroy the eye and has caused corneal perforation in a fatal case of *Candida* septicemia.[9] Histologically, the vitreous lesions are composed largely of polymorphonuclear leukocytes, macrophages, and epitheloid cells, but they can also harbor *Candida* organisms,[13,16,17,22,23] and Dan B. Jones, M.D., of Baylor College of Medicine has been able to culture them after four months of apparent inactivity of the disease (personal communication, May 9, 1979). Green, Jones, and Gentry isolated *C. albicans* from a rhesus monkey eye 110 days after intravascular inoculation.[24] These findings correlate with the remarkably late (four months) relapse of the infant described by Hill and associates.[7] In that case, the dormant lesion apparently lay invisible behind the iris until its reactivation by unknown factors. Such observations raise a question about attempting surgical aspiration of apparently inactive lesions, at least within four to six months after active infection. Stone, Irvine, and O'Connor[25] raised this question in their report of a poor outcome in one patient after vitreous biopsy of a *Candida* lesion. This is in contrast to the situation in exogenous *Candida* endophthalmitis, wherein vitrectomy has been reported to be effective.[26]

It is not known how long the organisms can continue to live in their vitreous matrix, nor how important an inhibiting role is played by the surrounding inflammatory reaction in the vitreous. Although the factors controlling the fungus/host balance in the vitreous are not entirely clear, the possibility of some benefit from an undisturbed vitreous body should be considered. It would seem that disruption of the colony and the surrounding host cellular reaction could disperse and reactivate the infection when the vitreous has not already been disturbed by surgery or trauma. The mere presence of the vitreous lesions in endogenous *Candida* endophthalmitis does not appear to be a clear indication for operation.

Addendum—Shortly after these two cases were observed, endogenous *Candida* endophthalmitis was discovered in another infant, at Texas Children's Hospital, Houston, by Helen H. Hittner, M.D. The infant, prematurely born, did not survive, and pathologic study confirmed the clinical diagnosis of endogenous *Candida* endophthalmitis, with multiple organ invasion by *Candida* organisms. Endogenous *Candida* endophthalmitis may not be as rare in infants as the small number of reported cases indicates.

Summary

Two infants recovered from endogenous *Candida* endophthalmitis. Case 1, to the best of my knowledge, is the first reported full term neonate with this entity. Free-floating vitreous opacities ("ballon vitréen") were found in one infant and the second infant's lesions resolved in a more conventional manner.

Acknowledgments

The artwork for Figure 2 was done by William M. Holmes. T. Borodofsky, M.D., and P. Whittington, M.D., provided the follow-up information for Case 1.

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EYELID AND ORBITAL CAVERNOUS HEMANGIOMA ASSOCIATED WITH KERATOCONUS

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Keratoconus is an axial ectasia of the cornea that has been associated with many systemic abnormalities and attributed to numerous causes; including degenerative, developmental, and local processes.[1] To the best of our knowledge, the association of an eyelid and orbital cavernous hemangioma and keratoconus has never been reported. We describe a case of a man with a hemangioma of the eyelid and orbit in which there was a direct relationship between the development of keratoconus and the pressure exerted on the globe by the tumor.

CASE REPORT

A 38-year-old man had a history of a mass on his left upper eyelid since age 3 years. He maintained that the mass had shown a slowly progressive growth throughout the years. He thought the growth may have been related to an asthmatic condition he had had since early childhood. He also complained of poor vision in his left eye, but was uncertain as to the time of onset.

On examination, the patient had an uncorrected visual acuity of R.E.: 6/9 (20/30) and L.E.: counting fingers at 2 feet. Visual acuity was corrected to 6/6 (20/20) in his right eye and his left eye improved to 6/9 (20/30) with −10.00 and a pinhole. Extraocular movements were intact and full. Exophthalmometry showed no proptosis. He had a severe blepharoptosis of his upper eyelid (Fig. 1) with 1 mm of levator muscle function. Using the frontalis muscle he could raise his upper eyelid 3 mm. A large mass was seen in the left upper eyelid (Fig. 2). The skin overlying the mass displayed a purplish discoloration with numerous telangiectasia. The mass was soft and could be ballotted retrograde into the orbit; it felt like a "bag of worms." The tumor did not increase in size with a Valsalva maneuver and no bruits were heard on auscultation. Clinically, it was thought to be a vascular tumor or a plexiform neurofibroma.

In the left eye, the conjunctiva was normal. The cornea had a conical ectasia (Fig. 3) with a positive Munson's sign (Fig. 4) on downgaze. There were numerous breaks of Bowman's membrane and an apical nebula. Keratometry was unsuccessfully obtained because the mires were totally off the keratometer. Applanation tonometry showed pressures of 14 and 12 mm Hg in the right and left eye, respectively. The anterior segment of the right eye was normal and no lens changes were evident in either eye. Results of ophthalmoscopic examination were normal in both eyes.

A- and B-scan ultrasonography showed a mass

Fig. 1 (Hornblass and Sabates). Frontal view showing severe blepharoptosis with a palpebral fissure of 1 mm.

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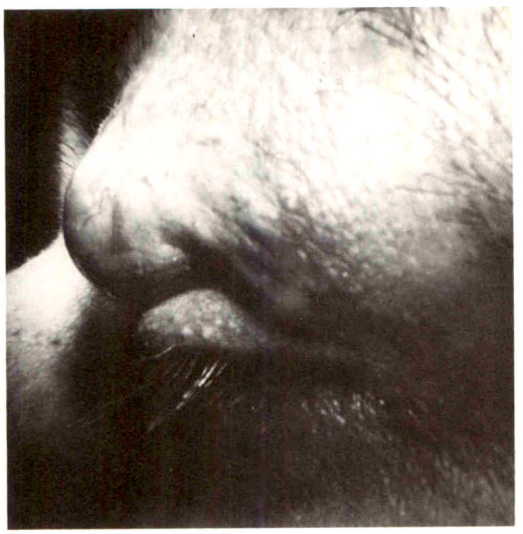

Fig. 2 (Hornblass and Sabates). Lateral view showing protrusion of the mass and telangiectasia on the skin surface.

Fig. 3 (Hornblass and Sabates). Conical ectasia of the cornea.

pressing on the left globe. It extended along the roof of the orbit and did not extend into the muscle cone.

Computed axial tomography revealed a mass extending between the globe and the roof of the orbit with a medial extension that displaced the lamina papyracea (Fig. 5, top left and right). The medial rectus muscle was markedly enlarged (Fig. 5, bottom left). Arteriography of the left orbit revealed displacement of the supraorbital artery but no feeder vessel to the tumor was evident.

An incision was made with a No. 15 Bard Parker blade through the superior crease of the left upper eyelid exposing the mass. It was freed from its surrounding tissues with sharp, blunt dissection with minimal bleeding. The mass extended along the roof of the orbit without invading the levator muscle nor the muscle cone (Fig. 6). It did, however, enter the orbit through the orbital septum.

The specimen consisted of a totally encapsulated purplish mass (Fig. 7) measuring 38 × 38 mm, which was spongy in texture. Histologic sections revealed vascular spaces lined by flattened endothelial cells filled with blood and thrombi in its lumen (Fig. 8).

Two months postoperatively (Fig. 9), the patient has 10 mm of levator muscle function and by using his frontalis muscle could elevate his left upper eyelid 14 mm. He is satisfied with the cosmetic appearance and has refused a corneal transplant.

Fig. 4 (Hornblass and Sabates). Positive Munson's sign on downgaze.

Discussion

Hemangiomas are the most common primary orbital tumors. Cavernous hemangiomas generally appear in the second to fourth decades of life and are usually located in the retrobulbar space, especially the intraconal area; thus, they clinically occur with proptosis. In our patient, the tumor was evident much earlier in life, and when examined he had an eyelid mass with progressive blepharoptosis. It did not affect the muscle cone, nor was there proptosis.

Keratoconus is a myopic axial ectasia, usually manifesting itself bilaterally; however, unilateral cases are also seen. It

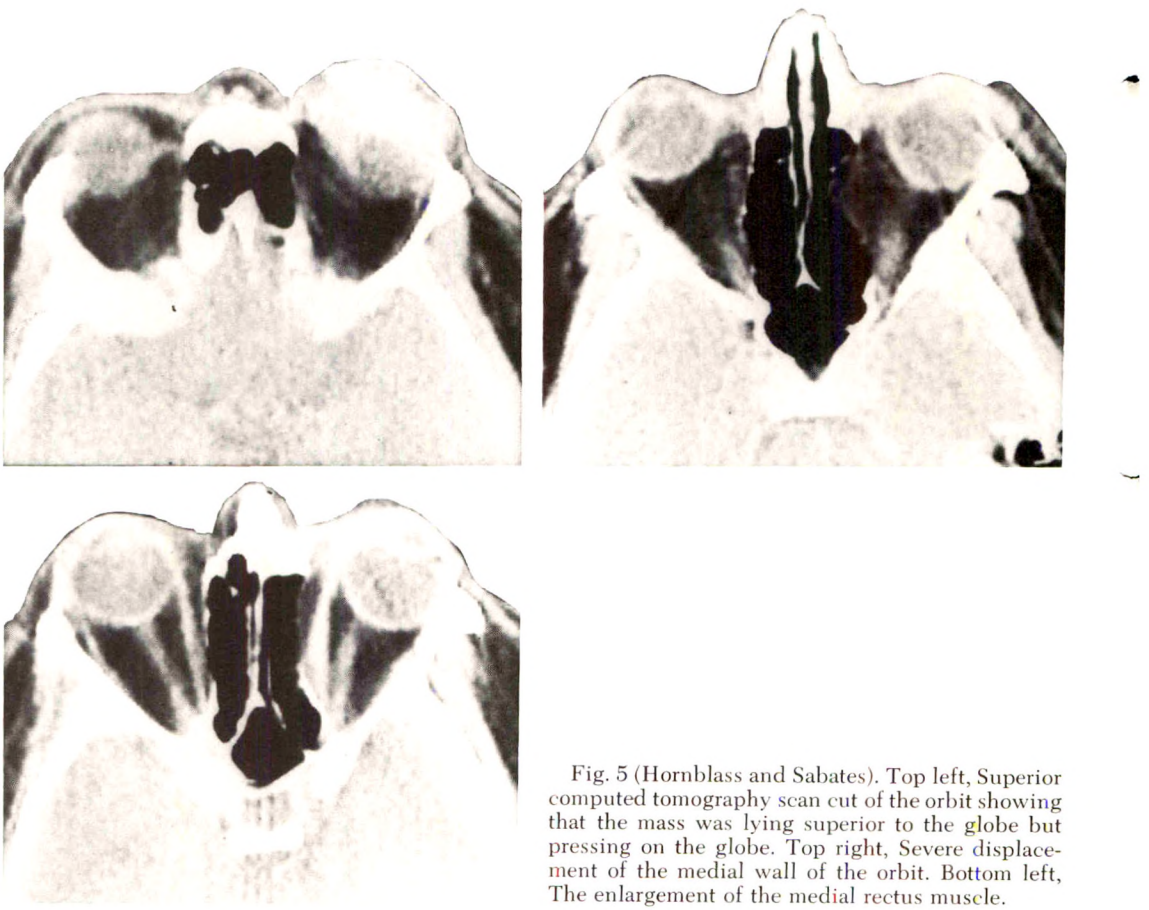

Fig. 5 (Hornblass and Sabates). Top left, Superior computed tomography scan cut of the orbit showing that the mass was lying superior to the globe but pressing on the globe. Top right, Severe displacement of the medial wall of the orbit. Bottom left, The enlargement of the medial rectus muscle.

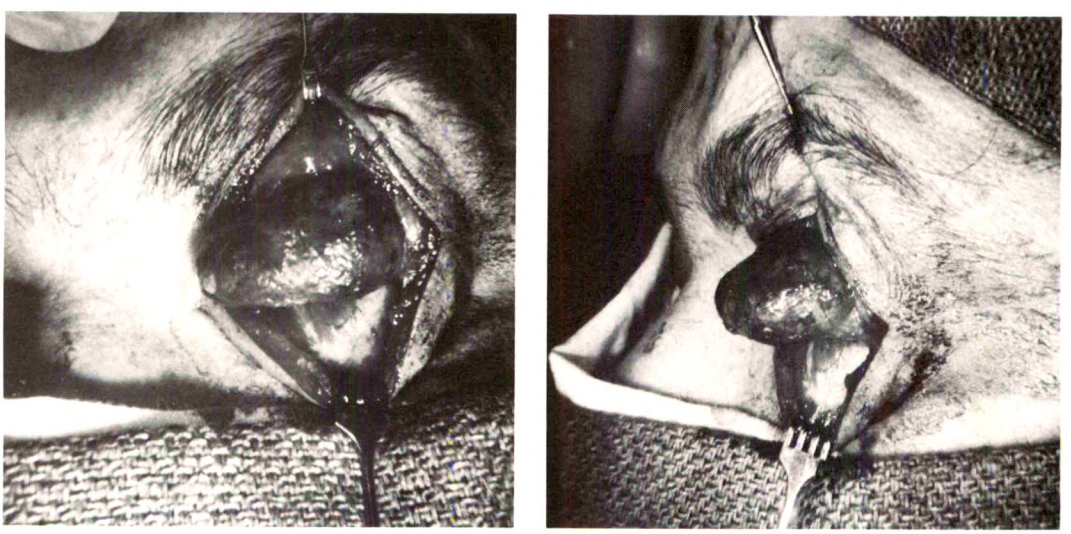

Fig. 6 (Hornblass and Sabates). Left, Frontal view of the tumor that sits on the globe. Right, Lateral view of the extent of the tumor.

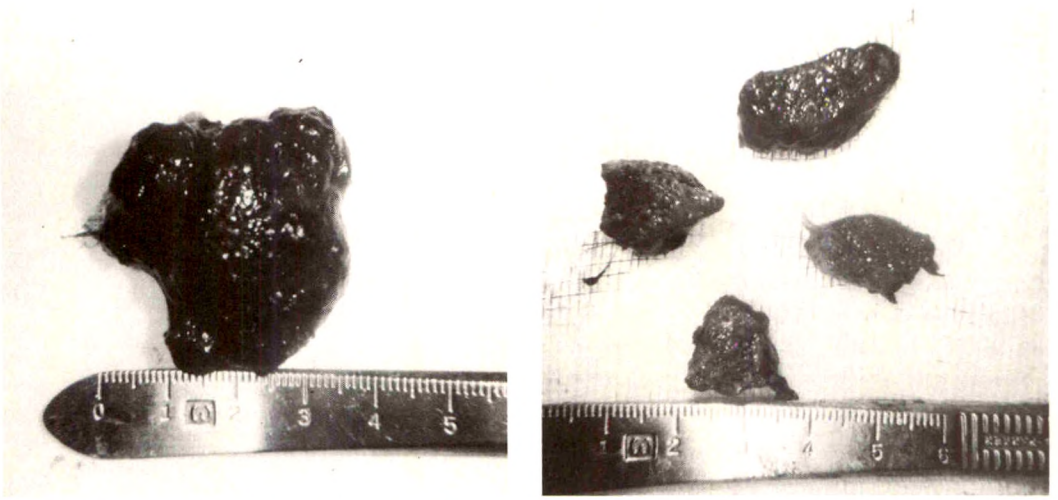

Fig. 7 (Hornblass and Sabates). Left, Totally encapsulated mass measuring 38 × 38 mm. Right, The tumor is sectioned and the cavernous nature of the tumor can be seen.

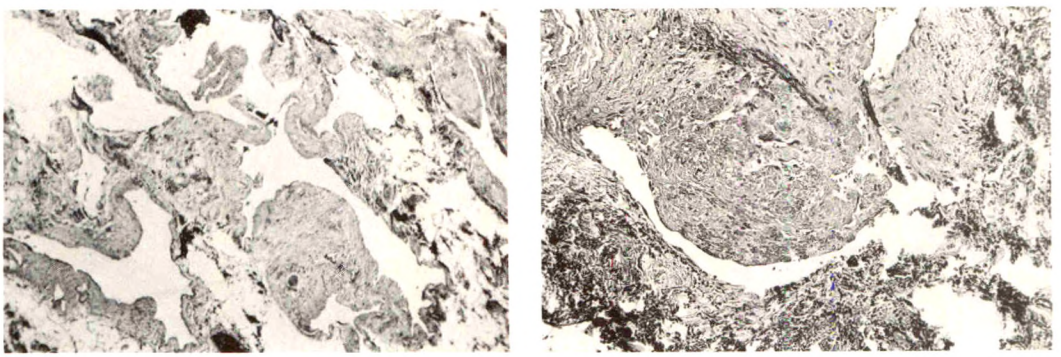

Fig. 8 (Hornblass and Sabates). Thrombi in the lumen, more on the right than on the left (hematoxylin and eosin, ×10).

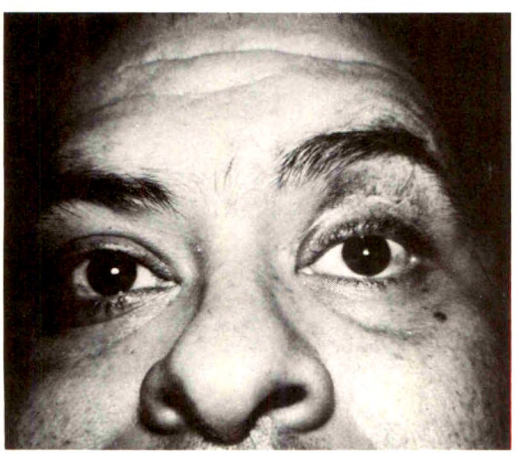

Fig. 9 (Hornblass and Sabates). Two months postoperatively; with the aid of his frontalis muscle, he looks cosmetically acceptable.

has been associated with many systemic abnormalities and it has been transmitted as a dominant or recessive trait. Local factors have been found to play a role in the development of keratoconus, especially the use of hard contact lenses and excessive eye rubbing in patients with atopic conditions.

Hartstein[2] in 1968, was the first to attribute the development of keratoconus to the prolonged wear of hard contact lenses in four patients. This theory has met with a great deal of skepticism; however, other authors have found a high incidence of hard contact lens wear before the onset of keratoconus.

Gasset, Houde, and Garcia-Bengochea[3] recently reviewed 162 cases of keratoconus and they found that 26.5% of the patients had previously worn hard contact lenses. They also studied 1,248 cases of soft contact lens wearers and only one developed keratoconus.

In 1970, Hartstein and Becker[4] postulated that an added factor was required of the host for the hard contact lens theory to be valid; namely, low ocular rigidity. They found that of those patients developing keratoconus many had low ocular rigidity. Gasset, Houde, and Garcia-Bengochea[3] found a significant difference in the ocular rigidity of 30 patients with and without keratoconus.

In 1967, Ridley[5] maintained that excessive eye rubbing could be a factor in the production of keratoconus. Other investigators have attempted to link the eye rubbing in atopic conditions to the incidence of keratoconus. Ruedemann[6] reported an incidence of allergy in 86% of his keratoconus patients. Gasset, Hinson, and Frias[7] reported excessive eye rubbing in 43% of their patients with keratoconus.

In our case, we believe that the prolonged pressure by the cavernous hemangioma on the globe for over three decades caused the keratoconus. However, the host must display a certain propensity and we believe that low ocular rigidity was a major factor.

Summary

A 38-year-old man had a 35-year history of a slowly progressive eyelid and orbital mass and keratoconus affecting his left eye. The mass was excised and found to be a large encapsulated cavernous hemangioma. We postulated a direct relationship between the development of keratoconus and the mechanical pressure exerted by the tumor on the globe.

Acknowledgment

Michael Tenner, M.D., provided neuroradiologic evaluation, and Alan H. Freedman, M.D., provided pathologic confirmation.

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CONGENITAL BLEPHAROPTOSIS, ANISOMETROPIA, AND AMBLYOPIA

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Our recent experience with patients who have congenital blepharoptosis of the upper eyelid has disclosed a high preoperative incidence of anisometropia, strabismus, and amblyopia. Although this association has been noted[1] (P. Diorio and A. C. Marrone, personal communication, 1979), it has not been stressed in clinical teaching or adequately described in published reports. In designing the present study to explore the relationship of congenital blepharoptosis to these conditions, we discovered an unexpectedly high incidence of postoperative astigmatic errors and amblyopia.

SUBJECTS AND METHODS

The clinical records of 65 patients with congenital blepharoptosis who had surgery between March 1975 and December 1978 were reviewed for this study. Patients with acquired blepharoptosis caused by trauma or oculomotor nerve palsy were excluded.

For the preoperative statistics listed, all 65 cases were included. However, because of loss to follow-up, postoperative data were lacking in several patients. For this reason, conclusions about refractive errors postoperatively were made from a smaller sample. From our data, supplemented with information that was obtained from communications with referring doctors, adequate follow-up records were obtained on 21 patients who had levator aponeurosis resections and 16 patients who had frontalis sling procedures.

Visual acuities were assessed in young patients by fixation behavior and in older patients with Allen cards, isolated or linear Snellen E testing, or lined letters depending on the patient's abilities. All patients described had two or more cycloplegic retinoscopies using 1% cyclopentolate HCl (Cyclogyl) or 1% atropine. Amblyopia was diagnosed by fixation behavior in the young patients and by visual acuity in the older patients.

We defined anisometropia as a refractive difference between the two eyes of at least 1.25 diopters of sphere or 1.0 diopter of cylinder. Although the spherical equivalent of these two criteria are not identical, these arbitrary dioptic limits seemed to be significant in clinical practice. Any refractive difference less than 1.25 diopters of sphere or 1.0 diopter of cylinder was considered insignificant or within range of error of the retinoscopy.

All patients had either a levator aponeurosis resection, a frontalis sling procedure, or both. One patient had a transconjunctival (Iliff) levator aponeurosis resection. Levator aponeurosis resections otherwise were done by a modified external (Berke) approach,[2] dissecting levator muscle from tarsus and conjunctiva without incising conjunctiva. A thin strip of eye bank sclera reinforced with Prolene suture was used for the frontalis slings. This strip was woven through the eyelid and eyebrow in a pentagonal configuration.

RESULTS

Preoperative examinations of 65 patients revealed anisometropia, strabis-

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mus, or amblyopia in 19 patients (Table 1). Most of these patients had varying combinations of these conditions; eight patients in this group had anisometropia by the criteria previously described. Interestingly, the more ametropic eye was always the eye with blepharoptosis.

With one exception, the nine patients who had a preoperative diagnosis of amblyopia also had an associated anisometropia or strabismus. The one exception was an 8-month-old child with severe, unilateral blepharoptosis. The clinical impression at the time was that the eye was amblyopic because of poor fixation despite a lack of demonstrable strabismus or anisometropia.

In the entire study, a total of 49 patients had unilateral blepharoptosis. Of the 49 patients—32 had a levator aponeurosis resection and 14 had a frontalis sling. Three had a levator aponeurosis resection followed by a frontalis sling. Sixteen patients in this series had bilateral blepharoptosis; four of these 16 had levator aponeurosis resections; 12 had frontalis slings.

Those patients who developed or increased their astigmatism postoperatively are listed in Table 2. In each case we have documented that this condition did not exist preoperatively. Each of the ten patients listed developed an astigmatism of 1.0 or more diopters in the operated eye or increased astigmatism by that amount.

Discussion

From our data we conclude that eyes with blepharoptosis frequently have associated functional abnormalities. A high incidence, 29% (19/65), of amblyopia, anisometropia, or strabismus was recognized preoperatively. With one exception, amblyopia always was associated with anisometropia or strabismus. Amblyopia always occurred in the eye with blepharoptosis.

Our data support those who have stated that blepharoptosis itself rarely causes an occlusion amblyopia.[1] However, in patients who are predisposed to developing amblyopia because of an associated strabismus or anisometropia, the presence of a blepharoptotic upper eyelid may contribute to the preference of the other eye for fixation or perhaps to the development of anisometropia.

An unexpected finding was that ten patients developed significant astigmatism in the operated eye after surgery. This occurred in four patients who had a levator aponeurosis resection and in six patients who had a frontalis sling. Unfortunately, because of the referral nature of the practice we do not have follow-up refractions on all of the patients postoperatively; therefore, determining a true incidence of astigmatism development in these 65 patients has not been possible. We can conclude only that the true incidence in this series was no lower than 11% for levator aponeurosis resections and 23% for frontalis slings, these percentages being the incidence of astigmatism if it is assumed that all patients lost to follow-up did not develop any astigmatism.

In the astigmatism that did develop the greatest corneal curvature was usually along the 90-degree meridian. Additionally, astigmatism developed in those patients who were believed to have acceptable cosmetic results. We could establish no relationship of the astigmatism to the presence of Bell's phenomenon, amount of levator aponeurosis resected (although most patients with congenital blepharoptosis had large levator aponeurosis resections), final eyelid position, preoperative strabismus, or refractive error. None of the patients were patched postoperatively because of the surgical procedures; no Frost sutures were used; ointments were used for only a short time.

The following case shows the extreme

TABLE 1

PREOPERATIVE ANISOMETROPIA, STRABISMUS, OR AMBLYOPIA*

Patient No.	Age at First Visit	Diagnosis	Visual Acuity	Cycloplegic Refraction	Surgical Procedure
21	7 yrs	Congenital blepharoptosis, R.E.; anisometropia	R.E.: 6/7.5 (20/25) L.E.: 6/12 (20/40)	R.E.: +2.25 +0.50 × 90 L.E.: +2.25 +1.75 × 90	Levator aponeurosis resection
42	5 yrs	Congenital blepharoptosis, L.E.; amblyopia; anisometropia	R.E.: 6/9 (20/30) L.E.: 6/24− (20/80−)	R.E.: +0.75 L.E.: −5.00 +2.00 × 180	Levator aponeurosis resection
33	3 yrs	Congenital blepharoptosis, L.E.; J-W, L.E.; double muscle elevator, L.E.; anisometropia	R.E.: 3/9 (10/30) L.E.: 3/9 (10/30)	R.E.: +2.00 L.E.: +2.00 +1.00 × 180	Restricted to elevation at surgery; frontalis sling, L.E.; levator muscle extirpation
8	6 mos	Congenital blepharoptosis, R.E.; anisometropia		R.E. +1.00 +1.50 × 105 L.E.: +0.50 +0.25 × 90	Levator muscle action 3 mm, R.E.; Berke levator aponeurosis resection
38	2 yrs	Blepharoptosis, R.E.; anisometropia	Normal	R.E.: +1.25 +1.50 × 80 L.E.: +0.75	Frontalis sling
9	2 yrs	Congenital blepharoptosis, L.E.; LET; amblyopia, L.E.		R.E.: −2.00 +1.75 × 120 L.E.: −2.50 + 1.00 × 60	Levator aponeurosis resection 22 mm
5	5 mos	Congenital blepharoptosis, R.E.; anisometropia; amblyopia, R.E.	Poor fixation, R.E.	R.E.:−10.50 +1.00 × 90 L.E.: −4.50 +1.25 × 50	Levator aponeurosis resection 18 mm
69	18 mos	Congenital blepharoptosis, L.E.; ET; amblyopia	Prefer R.E.	R.E.: +1.00 (postoperative) L.E.: +1.00	ET began at 1 yr of age; frontalis sling
66	2½ yrs	Congenital blepharoptosis, R.E.; RSO palsy; amblyopia, R.E., postoperative; RET, postoperative		R.E.: +0.25 +0.50 × 90 L.E.: +1.00 +0.50 × 90	Patched postoperatively; levator aponeurosis resection 25 mm
32	3 yrs	Congenital blepharoptosis, L.E. > R.E.; hydrocephalus; CP; ET	Prefer R.E.; later prefer L.E.	R.E.: +5.50 +0.75 × 45 L.E.: +4.50 +0.50 × 50	Levator aponeurosis resection 18 mm
31	2 yrs	Congenital blepharoptosis, L.E.; amblyopia, L.E.; ET	Prefer R.E.	R.E.: +3.00 L.E.: +3.00	Levator aponeurosis resection 20 mm

(Table continued on following page)

TABLE 1 *(Continued)*

PREOPERATIVE ANISOMETROPIA, STRABISMUS, OR AMBLYOPIA*

Patient No.	Age at First Visit	Diagnosis	Visual Acuity	Cycloplegic Refraction	Surgical Procedure
7	2 yrs	Congenital blepharoptosis, both eyes; congenital ET		R.E.: +0.50 +1.00 × 125 L.E.: +1.25 +0.50 × 75	Levator aponeurosis resection, both eyes, 19 mm
56	1 yr	Congenital blepharoptosis, L.E.; ET	Prefer R.E.	R.E.: +2.50 L.E.: +2.50	Frontalis sling, L.E.
3	1 yr	Congenital blepharoptosis, R.E.; ET	Prefer L.E.	R.E.: +0.50 +2.75 × 80 L.E.: −0.50 +2.25 × 110	Part-time patch, Berke 18 mm
4	2½ yrs	Congenital blepharoptosis, both eyes; accommodative RET; amblyopia; anisometropia		R.E.: +4.00 L.E.: +5.00 +1.00 × 90	Frontalis sling, both eyes; patched
51	1 yr	Blepharoptosis, both eyes; XT	Prefer L.E.	R.E.: +5.00 +0.50 × 125 L.E.: +5.00 +0.50 × 85	Frontalis sling, both eyes
39	3½ yrs	Blepharoptosis, R.E.; RIO palsy, R.E.; amblyopia, R.E.	Fix L.E.	R.E.: +2.50 +1.00 × 90 L.E.: +3.50 +0.50 × 80	Frontalis sling; RIO tuck; RSO tenotomy
1	2¾ yrs	Congenital blepharoptosis, L.E.; amblyopia; anisometropia	R.E.: 6/9 (20/30) L.E.: 3/9 (9/30)	R.E.: +2.25 L.E.: −0.50 +3.50 × 100	
34	8 mos	Congenital blepharoptosis, R.E.; amblyopia, R.E.	Objects to cover, L.E.	R.E.: +.50 L.E.: +3.50	Frontalis sling, R.E.

*J-W signifies jaw wink; LET, left esotropia, CP, cerebral palsy; RET, right esotropia; XT, exotropia; RIO, right inferior oblique muscle; RSO, right superior oblique muscle.

TABLE 2

POSTOPERATIVE ANISOMETROPIA, STRABISMUS, OR AMBLYOPIA*

Patient No.	Preoperative Diagnosis	Operation/Age	Preoperative Refraction	Postoperative Refraction/Age	Comments
27	Congenital blepharoptosis, L.E.	Levator aponeurosis resection 20 mos; levator aponeurosis 4 yrs	R.E.: +1.00 L.E.: +1.00	R.E.: +0.50 L.E.: −1.00 +3.50 × 90 4 1/2 yrs	R.E.: 45.75 × 90/46.00 × 180 L.E.: 44.25 × 180/50.50 × 90
26†	Congenital blepharoptosis, R.E.; CP	Levator aponeurosis resection 16 mos	R.E.: +2.50 +1.00 × 180 L.E.: +2.50 +1.00 × 180	R.E.: +2.25 +2.00 × 45 L.E.: +1.75 22 months	Developed intermittent XT
8	Anisometropia; congenital blepharoptosis, R.E.	Levator aponeurosis resection 4 1/2 yrs	R.E.: +1.00 +1.50 × 105 L.E.: +0.50 +0.25 × 90	R.E. +0.75 +4.00 × 105 L.E.: plano +1.00 × 90 7 1/2 yrs	
5	Congenital blepharoptosis, R.E.; anisometropia; amblyopia, R.E.	Levator aponeurosis resection 4 1/2 yrs	R.E.: −10.50 +1.00 × 90 L.E.: −4.50 +1.25 × 50	R.E.: −17.50 +6.00 × 120 L.E.: −3.00 +2.25 × 90 6 yrs	
57	Congenital blepharoptosis, R.E.	Frontalis sling 3 yrs	R.E.: +1.50 L.E.: +1.50	R.E.: +1.00 +1.75 × 90 L.E.: +1.00 7 yrs	
39	Congenital blepharoptosis, R.E.; RIO palsy; amblyopia, R.E.	Frontalis sling 3 yrs	R.E.: +2.50 +1.00 × 90 L.E.: +3.50 +0.50 × 80	R.E.: +2.25 +2.50 × 90 L.E.: +4.00 5 1/2 yrs	Patched, astigmatism present for two refractions, final refraction was plano, R.E.
6	Blepharoptosis, both eyes; blepharophimosis; epicanthus inversus	Frontalis sling, both eyes 1 1/2 yrs	R.E.: −1.00 +0.25 × 90 L.E.: +0.75 +0.50 × 90	R.E.: −3.00 +1.50 × 20 L.E.: −3.25 +3.00 × 115 11 yrs	Also had bilateral LR recess with upshift, equal vision, developed XT
50†	Congenital blepharoptosis, L.E.	Levator aponeurosis resection 3 years; frontalis sling 3 1/2 yrs	R.E.: +0.50 +0.50 × 90 L.E.: +0.50 +1.00 × 90	R.E.: +3.00 +1.00 × 180 L.E.: +3.00 +2.50 × 180 9 yrs	Patched, developed ET Later RNS: +3.00 +1.00 × 180 +3.00 +2.00 × 170 (Age 9 3/4 yrs)
17†	Congenital blepharoptosis, R.E.	Levator aponeurosis resection 2 yrs; frontalis sling 2 1/2 yrs	R.E.: +2.75 L.E.: +2.50	R.E.: +1.00 +3.25 × 115 L.E.: +2.50 +0.75 × 65 7 yrs	Patched, final visual acuity, R.E.: 6/9 (20/30), L.E.: 6/5 (20/16)
36†	Congenital blepharoptosis, L.E.	Frontalis sling 8 mos	R.E.: +1.50 L.E.: +1.50	R.E.: +1.50 L.E.: +0.50 +2.25 × 70 6 yrs	R.E.: 43.50 × 15/44.00 ×105 L.E.: 41.00 × 155/43.50 × 65 Patched, developed LET

*XT signifies exotropia; RNS, retinoscopy; ET, esotropia; LR, lateral rectus muscle; CP, cerebral palsy; RIO, right inferior oblique muscle; LET, left esotropia.
†Developed postoperative amblyopia.

to which the cylinder developed in one patient.

Case 27—A 20-month-old girl was first seen with minimal levator muscle function of the left upper eyelid. Refractive error was +1.00 in both eyes. At age 20 months an external levator aponeurosis resection of 18 mm in the left eye was done. At age 5 years a cycloplegic refraction was R. E.: plano and L. E.: −3.00 +5.00 × 90. At age 5 ½ years a repeat levator aponeurosis resection was performed because of dissatisfaction with the height of the eyelid. One month later a keratometry reading was R. E.: 46.00 × 180/45.75 × 90 and L. E.: 44.25 × 180/50.50 × 90.

More typically, the postoperative cylinders were smaller and varied slightly from one refraction to the other. The following case shows this point.

Case 57—A 5-month-old boy with severe congenital blepharoptosis of the right upper eyelid had a refractive error of +1.50 in both eyes. At age 3 years a frontalis suspension of the right upper eyelid was done. One month later his parents noticed his right eye was wandering, although this was not confirmed by motility evaluation. At age 3 ½ years the sling ruptured because of forehead trauma and had to be revised. At age 4 ½ years a cycloplegic refraction was R.E.: +1.00 +1.50 × 90 and L.E.: +1.50. Two years later it was R.E.: +.50 +2.50 × 80 and L.E.: +.75 +.75 × 100 and 1 ½ years later at age 7 years his refraction was R.E.: +1.00 +1.75 × 90 and L.E.: +1.00.

Of the ten patients who developed postoperative astigmatism, four developed amblyopia of a degree sufficient to require patching of the opposite eye. It seems apparent that astigmatism was the etiologic factor in these patients, and therefore, we speculate that there might have been more cases of amblyopia if surgery had been performed routinely earlier in the child's life. Blepharoptosis surgery is usually done here when the patient is about 4 years of age. The average age for the initial procedure in this series is 3.3 years. It is significant, therefore, that those patients who did develop amblyopia had surgery at an average age of 1 year and 8 months. The following case shows this point.

Case 17—A 10-month-old girl with congenital blepharoptosis of the right upper eyelid had an atropine refraction of R.E.: +2.75 and L.E.: +2.50. At age 1 ½ years she appeared to see well with both eyes. She adopted a head position with her head back and chin up to allow unobstructed binocular vision. At age 2 years an external levator aponeurosis resection of 25 mm was done on the right upper eyelid. Four months later she had a frontalis suspension procedure. At age 4 years, a cycloplegic refraction was R.E.: +.50 +3.25 × 110 and L.E.: +1.50 +1.50 × 65. The best visual acuity with this correction was R.E.: 6/21 (20/70) and L.E.: 6/9 (20/30). Patching of the left eye was begun. At age 6 years the cycloplegic refraction was R.E.: +1.25 +3.50 × 110 and L.E.: +2.50 +1.50 × 75. The eyelid position was believed to be satisfactory. Another retinoscopy 1 ½ years later revealed the same findings. On her last visit at age 7 ½ years best corrected visual acuity was R.E.: 6/9 (20/30) and L.E.: 6/5 (20/16). Stereoscopic acuity was 400 seconds of arc.

The following case shows a strabismus and more severe degree of amblyopia that developed with a small degree of astigmatism.

Case 50—A 3-year-old boy was first seen with congenital blepharoptosis in the left eye. His eyes appeared in good alignment to prism cover testing and he fused the Titmus fly. His cycloplegic refraction was R.E.: +.50 +.50 × 90 and L.E.: +.50 +1.00 × 90. At age 3 years he had an external levator aponeurosis resection in the left eye followed by a frontalis sling. For the next six years he was lost to follow up. When he returned at age 9 years, visual acuity was R.E.: 6/9 (20/30) and L.E.: 6/48 (20/160). A left esotropia was present. Cycloplegic refraction was R.E.: +3.00 +1.00 × 180 and L.E.: +3.00 +2.50 × 180. This patient was the only one who developed astigmatism against the rule (that is, corneal curvature greatest at 180 degrees). Occlusion therapy of the right eye was begun. Three months later he had a frontalis sling revision and a recession of his left medial rectus and a resection of his left lateral rectus. On his last visit at age 9 years 10 months, his visual acuity was R.E.: 6/5 20/16 and L.E.: 6/15 (20/50), and he had 10 diopters of esotropia.

We speculate that the surgical repositioning of the eyelid contributes to the astigmatism. In this series no patient developed a significant astigmatism in the unoperated eye. This factor and the fact that the astigmatism was with the rule (that is, corneal curvature greatest at 90 degrees in all but one case) suggests to us that the surgically elevated eyelid may be causing an abnormal pressure on the cornea and globe from above. This mechanism would be similar to the astigmatism caused by a large chalazion or by a hemangioma of the upper eyelid.[3]

Because anisometropia, even of small degrees, is likely to produce amblyopia in

a young child, the presence of upper eyelid blepharoptosis and the treatment of this blepharoptosis should alert the surgeon to the possibilities of amblyopia in that eye. None of our cases, however, showed the relief of existing astigmatism by blepharoptosis surgery, but rather the development of astigmatism or an increase in existing astigmatism after surgery on the blepharoptotic eyelid.

Many surgeons doing blepharoptosis surgery prefer to wait for such surgery until the patient has reached the preschool years because the assessment of the blepharoptosis can be more precise, the tissues available for its correction are more adequate, and social pressures are not as great until the child enters school. An even better reason for delaying surgery appears to be the increased potential for amblyopia with early surgery. Thus, a child with blepharoptosis but without amblyopia might be better treated at age 5 years than at age 2 years, even though the final eyelid position could be satisfactory at either age. However, parental pressures and other factors will continue to dictate the need for surgery in some younger children. When this is necessary, the surgeon should not judge the results of such surgery by eyelid position alone, but also by the presence or absence of astigmatism and amblyopia.

Summary

A review of the records of 65 patients who had surgery for congenital blepharoptosis of the upper eyelid during a three-year period revealed the preoperative presence of anisometropia, strabismus, or amblyopia in 19 patients. Postoperatively, ten of the 65 patients developed or increased their astigmatism in the operated eye. In four of these patients amblyopia attributed to this postoperative astigmatism developed. The results of our study suggest that blepharoptosis surgery done in the first few years of life may contribute to the development of astigmatism and amblyopia in some patients.

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PARS PLANA VITRECTOMY TECHNIQUES FOR RELIEF OF EPIRETINAL TRACTION BY MEMBRANE SEGMENTATION

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In the early stages of clinical application of pars plana vitrectomy to complications of proliferative diabetic retinopathy, the goals of surgery were to remove vitreous blood, reduce anterior to posterior vitreous traction on the retina, and to remove the vitreous scaffold on which proliferative tissue grows.[1] However, after this is accomplished, the vitreous surgeon is often faced with severe epiretinal fibrovascular proliferation that causes either distortion of the retina or contributes to persistent traction retinal detachment. Michels[2] found these two conditions present in 58% of 112 eyes in which vitreous hemorrhage obscured the posterior pole preoperatively. If only a simple vitreous hemorrhage was present, the rate of postoperative visual improvement was 85%; when the retina was distorted by fibrovascular tissue the visual improvement rate was 70% and decreased to only 39% when traction retinal detachment accompanied unresolving vitreous hemorrhage.

Because epiretinal fibrovascular proliferation limits the visual results of otherwise successful surgery, Machemer[3] introduced a two-instrument technique to remove these membranes. The end of a 22-gauge needle is bent and introduced into the eye after removal of all vitreous except that near the retinal surface. Under illumination from an instrument controlled with the other hand, this hooked needle is introduced beneath the edges of an epiretinal membrane and the membrane is slowly and gently peeled from the retinal surface. Most membranes have a point of tight adherence to the retina called an epicenter where separation is not possible. Membranes are peeled to these epicenters and then cut, leaving small tufts of tissue on the retinal surface. The technique of membrane stripping carries the inherent risk of creating retinal holes as attempts to peel away the membranes are made[4,5] and for this reason, some surgeons prefer not to attempt membrane stripping.[6] Additionally, some membranes are so tightly adherent that they cannot be removed by this approach.

Anatomic objectives of vitrectomy—As proliferative diabetic retinopathy develops, vascular and fibrovascular tissue emanating from the disk and optic nerve grows along the posterior hyaloid, becoming adherent to it. Tangential contraction of this tissue along the retinal surfaces causes a pleatlike folding and distortion of the retina. Adherence of the fibrovascular fronds to the posterior hyaloid is so firm that when the posterior vitreous detaches, the retina is pulled forward at these points of adherence, creating elevation of isolated fibrovascular fronds or traction retinal detachment (Fig. 1). Thus a posterior vitreous detachment in the diabetic patient creates a cone of vitreous extending from the vitreous base to the posterior pole.

The initial stages of pars plana vitrectomy for traction retinal detachment are performed to alleviate anterior to posterior vitreous traction.[2,7] The goal of surgery on epiretinal membranes is to relieve tan-

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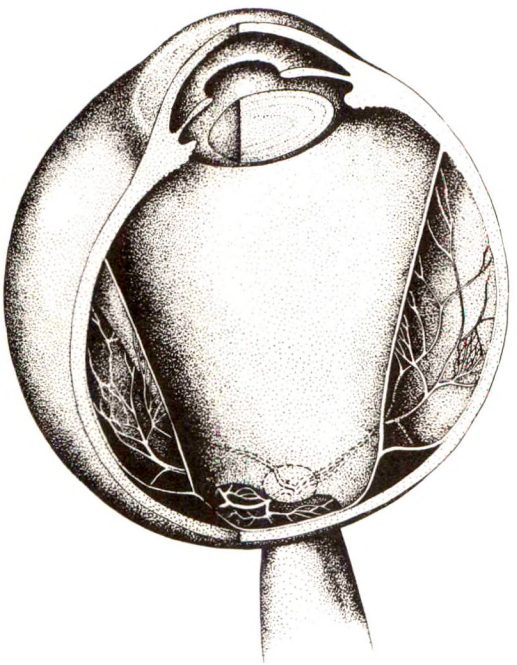

Fig. 1 (Meredith, Kaplan, and Aaberg). A taut cone of detached vitreous extends from vitreous base to points of adherence on posterior retina creating traction retinal detachment.

gential epiretinal traction that causes distortion of the macula and contributes to traction detachment.[7] Release of all traction and isolation of epicenters is important because residual membranes can contract in the postoperative period, thus causing subsequent late detachment and increased retinal surface distortion.

Surgical technique—Surgical approaches to epiretinal membranes may be done in cases where the media are clear and the macula has recently become detached,[2,5] or may be performed where distortion of the macula or traction retinal detachment is present when vitreous hemorrhage has been removed. Clear lenses are allowed to remain in place.[5] The initial stages of vitrectomy are performed to relieve anterior to posterior vitreous traction by using instrumentation that provides infusion, suction, and cutting capabilities combined with intraocular illumination. After removal of the anterior vitreous, the cone of vitreous extending from the vitreous base to the edge of proliferative tissue (Fig. 1) is circumscribed near its points of retinal attachment carefully, to avoid cutting underlying detached retina. Blood trapped behind the posterior hyaloid face or on the surface of the retina is removed.

Surgery on the retinal surface requires the availability of bipolar cautery,[8] intraocular scissors, and a hooked needle or special membrane picks. Careful assessment is first made of the structure of the fibrovascular membranes, and areas of persistent attachment of the posterior hyaloid to retina are noted. If cortical vitreous is not completely detached, it may be carefully separated from retina with membrane picks, a hooked needle, or intraocular scissors. Elevated, more solid areas may be gently sucked into the cutting port of the vitreous instrument and then pulled gently away from the retina, which often separates from it in large sheets. Freeing of cortical vitreous must be done over attached retina initially, working toward areas of detachment. Photocoagulation marks may be tenacious points of adherence of cortical vitreous to underlying retina and excessive traction can cause retinal breaks.

Fibrovascular bridging is frequently found between vascular arcades or between an epicenter along a vascular arcade and the optic nerve head. These membranes may be closely applied to retina or elevated as much as 5 to 7 disk diameters above the retinal surface. If separated sufficiently from the retinal surface, some bands may be safely cut with the vitrectomy instruments. Orientation of the cutting port anteriorly reduces the danger of suction on the underlying retina. Bipolar cautery with one lead connected to a light pipe and the other to the cutting instrument may be used on severely vascular membranes to close ves-

sels before severing them. Bleeding after cutting these vascular fronds usually stops spontaneously but can also be controlled by endophotocoagulating the cut vascular ends or by increasing the intraocular pressure by raising the height of the infusion bottle.

Sharp dissection with intraocular scissors—More commonly, fibrovascular sheets and cortical vitreous remnants are closely adherent to the surface of the retina. These sheets, especially when associated with thin detached retina, are best approached by sharp dissection with intraocular scissors. Use of the scissors has the advantage of not pulling on the retina. Because retinal breaks are most commonly produced by pressure on the retina, this risk of epiretinal surgery is significantly reduced by sharp dissection techniques.

Currently available scissors may be introduced through a 19- or 20-gauge incision and have a right angle configuration for approach to the retinal surface. More highly elevated bridging fronds or sheets are chosen for initial dissection (Fig 2, top left). The blades of the scissors are inserted beneath the areas of traction by finding a cleavage plane with the posterior blade used as a blunt dissector (Fig. 2, top right). Care is taken to avoid the retina with the tips of the scissors and not to draw it inadvertently between the cutting blades. Careful segmentation of the membranes allows the retina to settle back onto the pigment epithelium (Fig. 2, bottom left). Segmentation is meticulously carried out and multiple cuts are made to isolate all epicenters and relieve all traction. Heavy sheets that have caused a pleatlike effect, particularly near the disk, can be segmented toward the disk. (Fig. 3). Elevated vascular fronds may be isolated simply (Fig. 2, bottom left). Cut edges of membranes generally separate immediately during surgery but show increasing separation for several weeks during the postoperative period as the retina settles. Additionally, membranes retract or roll on themselves so their surface area is reduced. There is no need to drain subretinal fluid if no holes are present, because relief of traction is sufficient to allow reattachment of the retina.

Dissection techniques under air—The

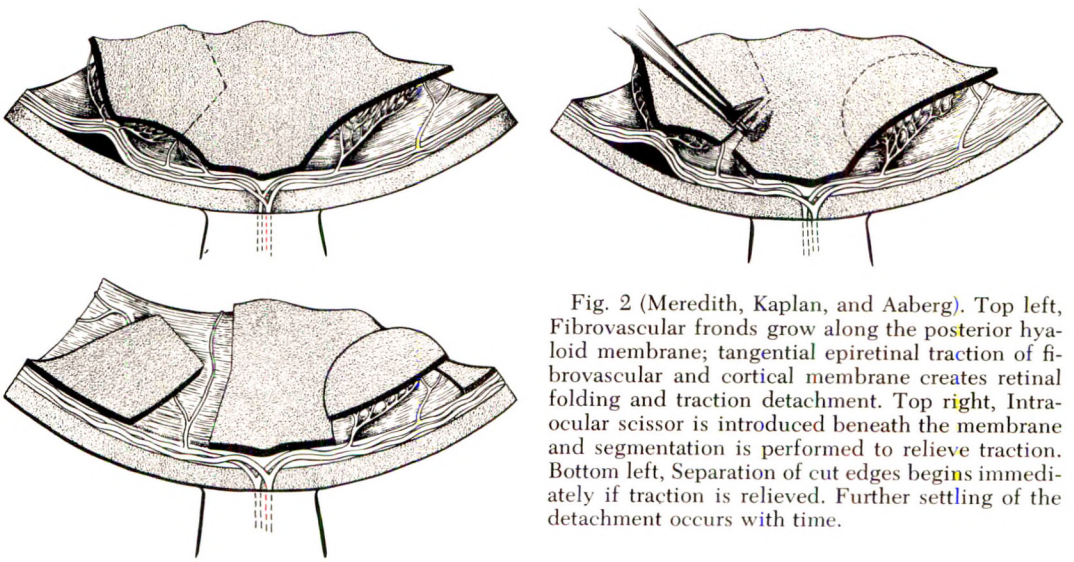

Fig. 2 (Meredith, Kaplan, and Aaberg). Top left, Fibrovascular fronds grow along the posterior hyaloid membrane; tangential epiretinal traction of fibrovascular and cortical membrane creates retinal folding and traction detachment. Top right, Intraocular scissor is introduced beneath the membrane and segmentation is performed to relieve traction. Bottom left, Separation of cut edges begins immediately if traction is relieved. Further settling of the detachment occurs with time.

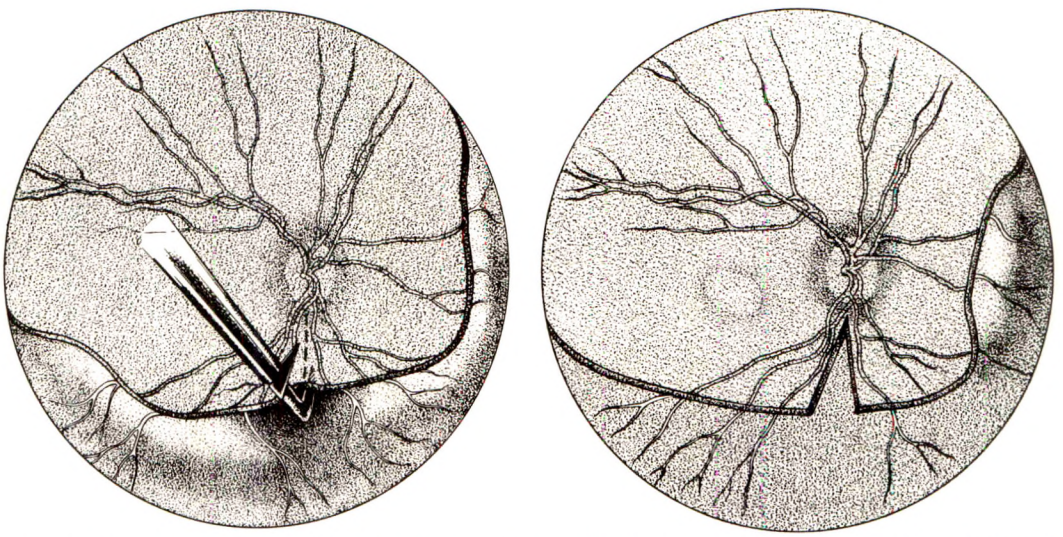

Fig. 3 (Meredith, Kaplan, and Aaberg). Surgeon's view of tabletop membrane over posterior pole. Radial cuts toward disk allow separation of pleated folds.

existence of a rhegmatogenous retinal detachment before surgery or creation of holes during epiretinal surgery, which leads to progressive intraoperative rhegmatogenous retinal detachment, make surgery particularly difficult and may prevent the achievement of the objectives of the vitrectomy. When it is highly mobile, attempts to work on the surface of the retina are hazardous. To solve this problem, air insufflation into the vitreous cavity may be used to reduce the mobility of the detached retina and permit continued dissection of epiretinal membranes. To accomplish this, a fluid-gas exchange (S. Charles, personal communication, June 1977)[2] is done by injecting air through the infusion line and allowing fluid to egress either through the vitrectomy needle or a fluted needle in the vitreous cavity. A 50-ml syringe filled with air is attached to the infusion line and the eye is gradually filled with air. If significant subretinal fluid caused by a retinal break is present, the tip of the fluted needle is placed within the hole as suggested by Charles (S. Charles, personal communication, June 1977). As air is injected, fluid will be forced out of the subretinal space, thereby flattening the retina. In unusual instances where large amounts of fluid are present but no hole is seen, creation of a hole in an area where it can be easily repaired may allow this internal drainage procedure. Once the vitreous cavity is filled with air, vitreous scissors are introduced. Continued slow infusion of air is necessary to maintain sufficient intraocular pressure to prevent corneal striae and keep the retina flattened. Many small air leaks in this system are present, but the most significant occurs through the hollow hub of the vitrectomy scissors, thereby requiring a constant infusion of air. At the conclusion of the segmentation of membranes and release of epiretinal traction, the vitreous cavity can remain filled with air or a 30% sulfahexafluoride and air mixture can be used to replace it if continued internal tamponade is desired.[9,10]

The same technique has also been used to separate taut posterior membranes that were otherwise inoperable. The infusion

of air into the vitreous cavity puts pressure on the detached retina and displaces it posteriorly, increasing the separation between retina and the proliferative tissue. These manipulations under air are optimally performed in the aphakic eye because of the multiple white reflexes present when the vitreous cavity is filled with a gas in the phakic eye. If air insufflation for this manipulation is anticipated, removal of the lens is almost always necessary. A contact lens is not necessary for posterior work when the aphakic eye is completely filled with air. The optical image created by an air-filled vitreous cavity is lessened, but this has not proved to be a significant technical problem. The quality of the image is variable if the eye is allowed to soften transiently because of corneal striae but a slow continuous infusion is usually sufficient to overcome this problem.

Management of complications—Retinal breaks are the main complication of surgery on epiretinal membranes. Diathermy too close to the retina can cause full-thickness necrosis and retinal holes. Because peeling procedures necessitate some pulling on the retina, the incidence of retinal tears has been shown to be increased from 12 to 24%.[4] These holes are usually posterior, and although their incidence is decreased with sharp dissection techniques by using intraocular scissors, posterior breaks may still occur. Because epicenters of vitreous traction frequently occur at the margin of ischemic areas where new vessels take their origin, the epicenters are adjacent to the thinnest and most atrophic retina, and manipulations in these areas have increased hazard. Additionally, once the epiretinal traction has been relieved, mechanized suction cutters should not be used to attempt to remove epiretinal tissue, because the newly mobile retina may be quickly aspirated into the cutting port, thus creating large breaks.

Management of posterior retinal holes depends on the amount of adjacent epiretinal traction remaining and the extent of the associated rhegmatogenous retinal detachment. When little or no traction is present and the rhegmatogenous detachment is minimal, the tear may be surrounded with intraocular photocoagulation or intraocular cryotherapy. Creation of a chorioretinal lesion with these intraocular delivery systems is easier and more accurate in far posterior breaks. The eye may then be filled with gas to provide internal tamponade[2,3,9] using air or 30% sulfahexafluoride.[10] Scleral buckling is unnecessary if no adjacent traction is present to reopen the hole.

If significant traction cannot be relieved adjacent to the retinal break, external buckling is necessary, but may be exceedingly difficult with tears in the posterior pole. Use of a radial exoplant silicone sponge is helpful in these instances. If one half to one full quadrant of detachment is present, intraocular cryotherapy is often difficult and endophotocoagulation is usually impossible. In this instance, the lens is removed and internal drainage of subretinal fluid and insufflation of the vitreous cavity with air of sulfahexafluoride is performed as previously described. Either endophotocoagulation or endocryotherapy can now be performed in conjunction with external buckling. Care must be taken to have the endophotocoagulator tip immersed in a slight meniscus of fluid to avoid damage to the fiberoptic tip.

Injury in rabbit eyes causes membrane formation,[11] making it an ideal model for practice surgery. Experience in the animal eye allows the operator to gain skill with two-instrument techniques, intraocular diathermy, cryotherapy, endophotocoagulation, and sharp dissection with intraocular scissors. Such manipulations in laboratory animals should be done before undertaking difficult technical problems in human diabetic patients.

Summary

We used a technique for surgical management of fibrovascular membranes to relieve epiretinal tangential traction when present in proliferative diabetic retinopathy. Sharp dissection with intraocular scissors was used to segment fibrovascular and cortical vitreous membranes together with cauterization of large vessels with intraocular bipolar diathermy. The objective of membrane segmentation was to relieve all epiretinal traction, thereby reducing retinal surface distortion and allowing the retina to flatten and reattach. Complete relief of traction prevented further late contraction of membranes and subsequent distortion and redetachment.

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HEREDITARY VITREORETINAL DEGENERATION, CLEFT LIP AND PALATE, DEAFNESS, AND SKELETAL DYSPLASIA

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Hereditary vitreoretinal degeneration may be associated with various systemic skeletal abnormalities. The median cleft face syndrome is the most commonly associated defect.[1,2] No strong tendency apparently exists for the association of cleft palate with hyaloideoretinal degeneration and skeletal abnormalities, but its occurrence in familial cases suggests that such associations may be causal.[3] In studying a family with this association we found undescribed features that emphasize the range of the clinical anomalies and the phenotypic spectrum of this condition.

CASE REPORTS

Case II-1—We first saw this 26-year-old man (Fig. 1) in 1972 when he was hospitalized because of a two-day history of loss of vision in his right eye. Ocular examination disclosed severe myopia in both eyes. The visual acuity was R.E.: 1/60 (3/200) with −12.0 sph; and L.E.: 6/12 (20/40) with −10.0 sph. The pupils were round and reacted to light and to near fixation. On slit-lamp examination the corneas were clear and the angles were normal. Mild, posterior cortical and subcapsular cataracts were present in the anterior segments in both lenses. The intraocular pressure was R.E.: 10 mm Hg and L.E.: 17 mm Hg. Ophthalmoscopy of the right eye disclosed a retinal detachment in an optically empty vitreous cavity. The detachment was situated in the upper portion. Five retinal tears were located both nasally and temporally at various distances from the corneoscleral limbus. One of the horseshoe tears had rolled edges with a visible vitreous membrane attached to its flap. The fundus of the left eye also had an optically empty posterior vitreous cavity, a fibrillar anterior vitreous, and a few preretinal membranes. The retina itself was attached but had a marked meridional fold between the 2 and 4 o'clock positions. Latticelike degeneration with disseminated patchy areas of thinned pigment epithelium was present in the equator region.

Three circling buckling operations, followed by photocoagulation, were done in the right eye to obtain successful anatomic reattachments. In the left eye a big tear in the upper nasal quadrant was photocoagulated in 1973. Despite this treatment and careful follow-up, the patient developed a left temporal retinal detachment caused by two retinal tears. Retinal reattachment was obtained after four different surgical procedures. At his last examination, after six years of follow-up, he had a corrected visual acuity of R.E.: 6/30 (20/100) and L.E.: 6/20 (20/60), as the result of bilateral macular puckering. The electroretinograms showed decreased amplitude responses of both photopic and scotopic components but peak latencies were preserved (Fig. 2,C.)

The patient had had a surgical correction of complete cleft palate and cleft lip (Fig. 3) at age 4 years. A maxillary hypoplasia caused a flattened midface (Fig. 4). Because of the associated vitreoretinal degeneration and cleft palate, an extensive medical examination was initiated to rule out any other systemic diseases. Results of all routine laboratory tests were within normal limits. The physical examination disclosed thoracic kyphosis, bilateral pes planus and adductus, and calcanea valgus. The finger, wrist, and ankle joints were hyperextensible (Fig. 5). Radiographic examinations of the skeleton disclosed the following abnormalities: lumbal hyperlordosis, a flattened L-5 vertebra, bilateral triangular navicular bone, medial deviation of the tarsal bones of the left foot and bilateral synphalangism of proximal joints of the second, third, and fourth toes. A broad pelvic bone with feminin form was found (Fig. 6). An audiologic examination showed a high frequency sensorineural hearing defect with increased compliance of the middle ear, which had not progressed since an earlier examination.

Case II-3—This 22-year-old man (Fig. 1), the younger brother of the proband, was examined. Ocular examination showed normal external eye movements, and intraocular pressures. The lenses were clear and the angles were within normal limits. Visual acuity was R.E.: 6/12 (20/40) with −5.0 sph and L.E.: 6/9 (20/30) with −4.0 sph. Ophthalmoscopy disclosed vitreous membranes and optically empty vitreous cavities. In the retina of the right eye pigmented scars resulting from photocoagulation were found in the upper temporal side. The treatment had been done two years previously in another hospital because of a retinal break. In both eyes latticelike degenerations were found in the equatorial region. The retina in these areas looked slightly

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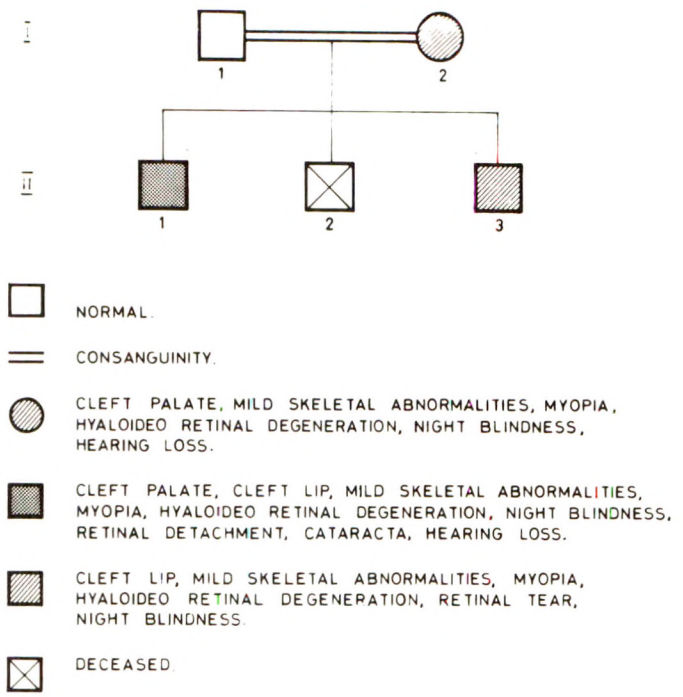

Fig. 1 (Regenbogen and Godel). Family pedigree.

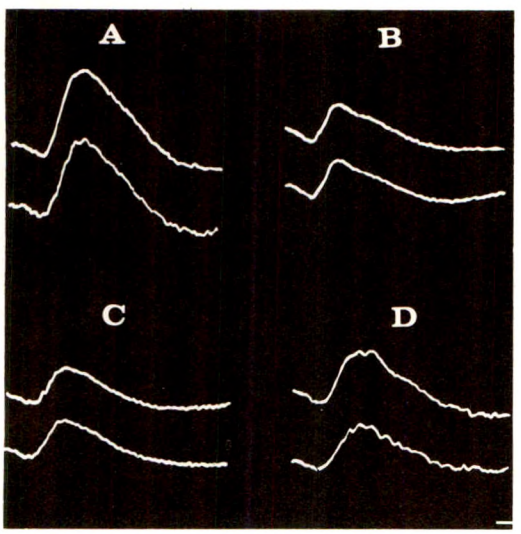

Fig. 2 (Regenbogen and Godel). The impaired electroretinograms of the mother (B) and the two children (C,D) as compared with the normal electroretinograms of the father (A) (calibration, 200 μV, 40 msec).

Fig. 3 (Regenbogen and Godel). Oral scars after the surgical correction of the cleft palate.

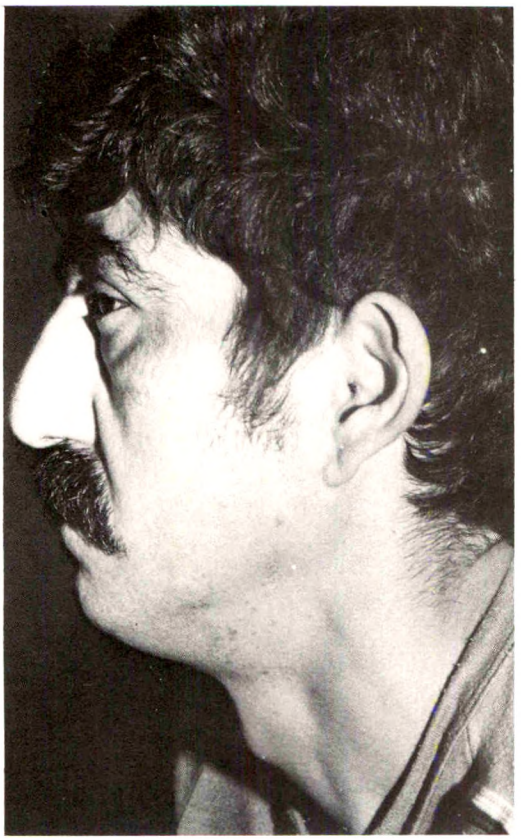

Fig. 4 (Regenbogen and Godel). Profile view with midfacial flattening and short mandible.

elevated and had lost its transparency. Scattered areas of thinned pigment epithelium with exposure of the large choroidal vessels were found.

The patient complained of visual difficulties toward nightfall and his electroretinograms showed smaller amplitude responses with moderately reduced scotopic activities (Fig. 2,D).

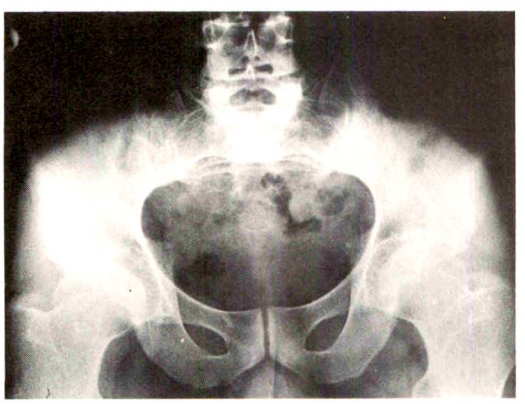

Fig. 6 (Regenbogen and Godel). Broad pelvis with feminine form.

Fig. 5 (Regenbogen and Godel). Hypermobility of joints.

A general physical examination of the patient showed a surgically corrected cleft lip and a highly arched palate. Pectus excavatum and laxity of the finger, wrist, and ankle joints were found. Skeletal x-ray films disclosed lumbar hyperlordosis.

Case I-2—The 51-year-old mother (Fig. 1) of the previously described patients was also examined. Ocular examination disclosed visual acuity of 6/12 (20/40) with −7.0 sph in each eye. She was unaware of any ocular diseases but complained of night blindness. Ocular pressure and chamber angles showed no abnormalities. White specks on the surface of the embryonic nucleus were found in the lens. Ophthalmoscopy showed translucent vitreous strands moving freely in the optically empty vitreous cavity. In the equatorial region of the retina, small areas of yellow atrophy were present with sheathed retinal vessels but without any pigmentation. The electroretinogram showed subnormal amplitudes but normal latencies of its positive components, indicating significantly inferior scotopic activities (Fig. 2,B.)

She had had a surgical correction of cleft palate in childhood. Results of routine laboratory studies were normal. The x-ray studies revealed broadening of the metatarsal and metacarpal joints. There was a laxity of the hand joints. Audiologic examination showed a bilateral high frequency sensorineural hearing defect with a small conductive component. The remainder of the findings, including the neurological status, were normal. The family history disclosed that her father was 44 years of age at her birth. Neither parent had any particular diseases.

The patient had another child who developed meningitis and died at 4 years of age. This child had

no midline fusion defects. All of the patient's pregnancies were uncomplicated and there was no exposure to teratogenic agents. She did not mention any difficulties regarding the birth of her children. She and her husband were first cousins. Her husband had normal results from physical, ocular, and laboratory examinations.

Discussion

A variety of skeletal abnormalities have been discovered in patients with hereditary vitreoretinal degenerations of various types.[4–6] Most are inherited in an irregular autosomal dominant manner. The most characteristic disease is a hereditary arthro-ophthalmopathy, which is a dominantly inherited connective tissue disorder consisting of progressive multiple dysplasia of the epiphyses associated with overtubulation of the long bones. Some of the skeletal anomalies found in our cases, such as cleft palate, hypermobility of joints, flattened vertebral bodies, and pelvic bone deformities, were identical with those described in Stickler syndrome. But the lack of the characteristic progressive irregular flattening of the articular surfaces, and marked enlargement of the elbows and knees, made a diagnosis of Stickler disease unlikely. The sensorineural deafness in our two patients, which is sometimes present in the Stickler syndrome, was unusual, suggesting that the associated ocular vitreoretinal degeneration and skeletal abnormalities have a complex dysmorphogenesis. All our involved patients had similar sensorineural hearing loss in the high frequency range.

This association of symptoms in such a rare syndrome indicates that this condition results from a phenotypic variability of genic origin, and the full complement of defects described in our family places this association in the class of vitreoretinal skeletal syndromes.

The ocular findings in our family were characterized by an optically empty posterior vitreous, a fibrillar anterior vitreous, preretinal membranes, and retinal breaks. In the proband the simultaneous multiple retinal tears situated in different meridians and distances from the corneoscleral limbus led to retinal detachment with poor surgical prognosis, confirming earlier clinical impressions.[4,7] The bilateral cortical cataract in the proband was at variance with the usual nuclear cataract described in vitreoretinal degeneration,[5] and the night blindness present in all the involved cases was characteristic of the syndrome.[4]

Symptoms were present in members of two successive generations in our family. The appearance of the symptoms in the mother, the only affected child of a previously unaffected family, suggests that she carried a fresh gene mutation. The advanced age of her father at the time of her birth would support this idea.[8] The subsequent transmission of this syndrome to two children suggests a dominant inheritance. Consanguineous matings do not increase the incidence of dominantly inherited diseases; thus, the marriage between the heterozygote mother and the phenotypically normal father did not influence the remarkable variability in gene expression between the brothers. However, from the presence of such symptoms, it is not possible from this pedigree to determine whether the expression of the same mutant gene produces the syndrome or whether multiple alleles or mutations of separate loci are involved.

Because of the broad range of expressivity, the similarity in clinical manifestations, and the mode of inheritance, some investigators believe that these are closely related entities.[9,10] Enough genetic evidence exists to support the conclusion that the mode of inheritance does not help to distinguish these disorders because they are almost all autosomal dominant.

Summary

Two brothers and their mother had vitreoretinal degeneration associated with

cleft palate, a peculiar physiognomy, skeletal anomalies, and sensorineural deafness. The pattern of inheritance in this family suggested autosomal dominant transmission.

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Ophthalmic miniature

A deficiency of the black pigment of the eye is occasionally found in persons of a very fair complexion and light hair. This affection is therefore common in the Albinoes. This circumstance arises from the whiteness of the eyelashes and hair, whereby the retina is deprived of the natural shade that softens the light in its descent. This debilitated race generally inhabit warm and damp regions; they are seldom long-lived, and frequently low-spirited and morose. The iris is of a pink colour, and this circumstance, added to the constant winking that the weakness of the organ occasions, gives them a distressing appearance. In horses, this want of the dark pigment constitutes what is called the wall eye.

J. G. Millingen
Curiosities of Medical Experience
London, Richard Bentley, 1839

BILATERAL ACUTE RETINAL NECROSIS

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Bilateral acute retinal necrosis begins as a symmetrical and confluent retinal swelling with hemorrhages. It develops into necrosis and sloughing of the retina into the vitreous. This disease process appears to be secondary to an obliterative vasculitis of the retina, and it is accompanied by an anterior uveitis. Destruction of the retina is rapid, lasting only a few weeks in each eye.[1,2]

We describe a patient who had complete retinal destruction in one of the two eyes involved. No systemic abnormalities were found in this case and no cause was identified.

CASE REPORT

A 20-year-old woman had a three-week history of soreness in the back of her mouth that gradually spread to include the whole left side of her face, as well as a left frontal headache for one week, and progressive blurring in the left eye for three days. Examination on Sept. 3, 1978, showed tenderness over the left frontal, temporal, maxillary, and orbital areas, as well as the ascending ramus of the mandible. She had a low-grade fever up to 37.8°C. No signs of infection or ulceration were found. Results of her neurologic examination were normal except for redness of the conjunctiva and a dilated and fixed pupil in the left eye. Ophthalmoscopic examination of the left eye showed disk edema, venous engorgement, and peripheral retinal hemorrhages.

The working diagnosis was a facial infection, possibly secondary to a sinusitis with secondary venous thrombosis in the left eye. She was treated with penicillin. Laboratory examination included the following: x-rays of her skull, sinuses, and chest; computed axial tomography with and without contrast; blood cultures; urine cultures and cerebral spinal fluid cultures for bacteria and fungi; all results were negative. She had an erythrocyte sedimentation rate of 13 mm/hr, a hemoglobin of 14.4 g/dl, a white blood cell count of 9,300/mm^3, and a red blood cell count of 4.9×10^6/mm^3. Her spinal tap suggested a viral, or nonspecific low grade inflammation with a normal opening pressure, a red blood cell count of 34/mm^3; and a white blood cell count of 14,000/mm^3 with a differential of 79% lymphocytes and 21% polymorphonuclear leukocytes. The protein level was 30 mg/100 ml and the glucose was 55 mg/100 ml with a blood glucose level of 117 mg/100 ml.

She was transferred here where she was seen on Sept. 8, 1978. On examination, her best corrected visual acuity was R.E.: 6/4.5 (20/15) and L.E.: light perception. Results of external and biomicroscopic examinations were normal in the right eye and no follicles or papillae were seen in either eye. The conjunctiva on the left was +2 hyperemic, the pupil was fixed at 7 mm, and biomicroscopic examination showed signs of an anterior uveitis with 1.5 fine, medium, and greasy keratic precipitates, 2 flare, 3.5 cells,[3] no synechiae, and no cells in the vitreous. Intraocular pressure was R.E.: 8 mm Hg and L.E.: 14 mm Hg.

Results of ophthalmoscopic examination of the right eye were normal (Fig. 1). Ophthalmoscopic examination of the left eye showed hemorrhages in all quadrants, edema of both the retina and the nerve head, and dilated and irregular vessels. The

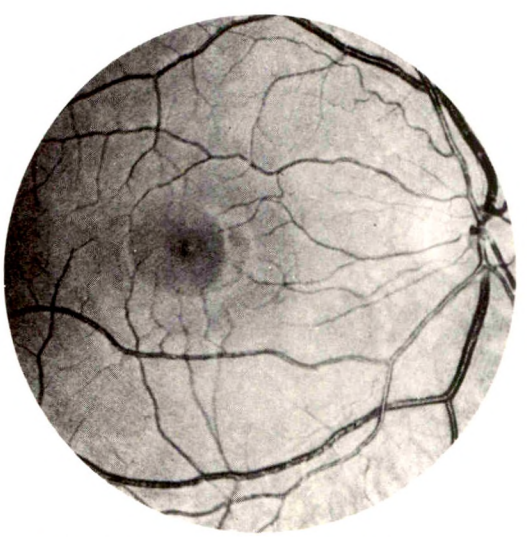

Fig. 1 (Price and Schlaegel). Kodachrome of the right eye on Sept. 8, 1978, showing a normal fundus.

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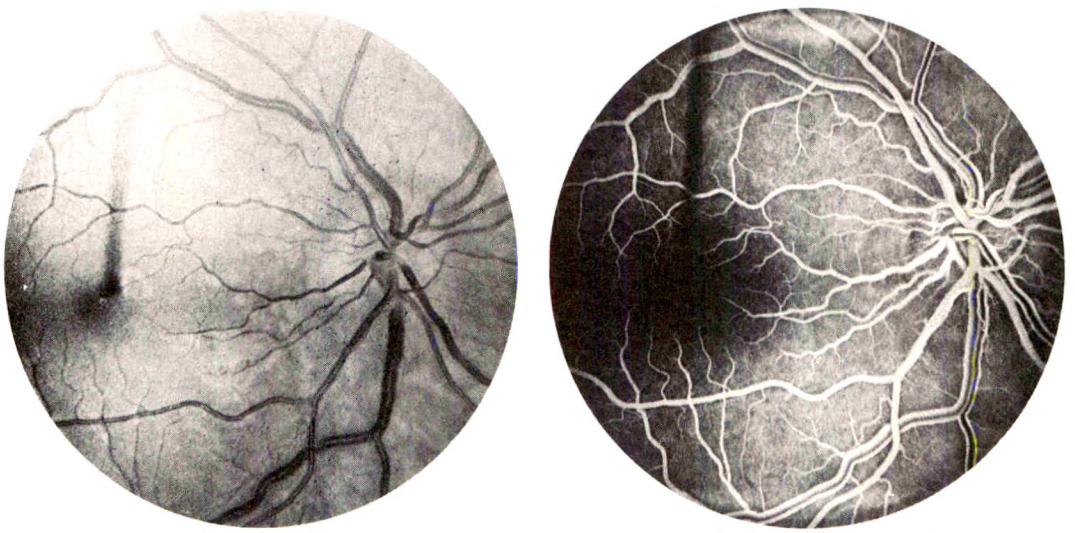

Fig. 2 (Price and Schlaegel). Two views of the right eye on Sept. 20, 1978. Left, A Kodachrome. Right, A fluorescein angiogram in the late venous phase showing a mild dilation of the vessels and tortuosity of the veins not present on Sept. 8, 1978. The posterior pole is otherwise normal.

fluorescein angiography of the left eye showed a diffuse leakage of all retinal vessels with obliteration of flow in some.

No cause for her vasculitis could be found and no treatment was given. The obliterative nature seemed to be similar to that reported in Behçet's disease,[4] although there was no history of ulcerative lesions, arthralgias, phlebitis, or erythema nodosum. Her history was noncontributory with respect to immunizations, travel, recent upper respiratory tract infection, and toxic or chemical exposures. She had a normal full-term infant in May 1978. She had had frequent sore throats during her pregnancy.

On Sept. 19, 1978, she began to have supraorbital pain on the right. Visual acuity decreased to R.E.: 6/6 (20/20) and L.E.: no light perception. The anterior chamber was still quiet on the right, whereas that on the left showed an increased reaction, as well as retrolental and anterior vitreous cells. Ophthalmoscopic examination of the right eye revealed a mild increase in haze and dilation of some veins (Fig. 2). Fluorescein angiography also showed the increased vessel size, as well as peripheral arteritis (Fig. 3). We treated her for Behçet's disease because the vasculitis was spreading to the right eye. She was given 10 mg of chlorambucil daily as reported by Mamo.[5]

By Oct. 2, 1978 (two weeks after the onset of symptoms in the right eye), her visual acuity had decreased to hand movements at 4 feet. She was given 300 mg of prednisone and 15 grains of aspirin every morning as a last attempt to reverse the vasculitis. There was now a full blown anterior uveitis in the right eye with +2 fine, medium, and greasy keratic precipitates, 3 flare, 3.5 cells, and no synechiae. Cells were present in the vitreous. She had diffuse retinal hemorrhages and edema in the right eye (Fig. 4), and fluorescein angiography revealed a severe obliterative vasculitis with little perfusion more than three to four disk diameters from the disk (Fig. 5). Hemorrhages in the left eye were clearing, leaving white gliotic vessels.

On Oct. 18, 1978, visual acuity in the right eye was still hand movements at 4 feet. The anterior chamber examination showed no change, and the fundus and fluorescein examinations showed essen-

Fig. 3 (Price and Schlaegel). Right eye, Sept. 20, 1978. Fluorescein angiogram of a peripheral inferotemporal arteriole showing leakage and late staining with dilation. Earlier frames showed the dilation to be irregular.

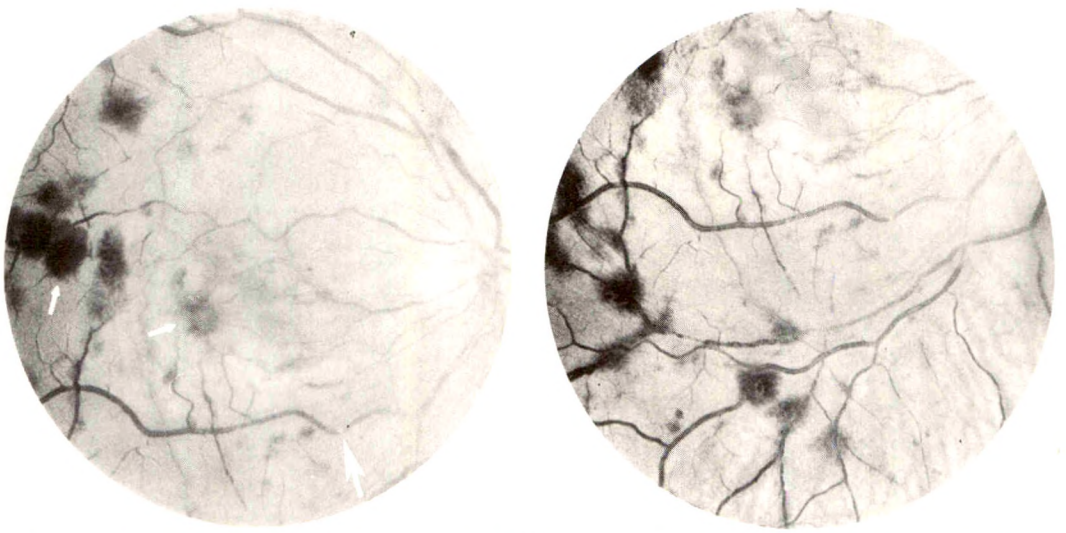

Fig. 4 (Price and Schlaegel). Right eye, Oct. 2, 1978. Left, Kodachrome now shows abrupt vessel dilation in an inferior temporal arteriole (large arrow), macular edema, and multiple hemorrhages (small arrows). The light spot at the above site of dilation appears to be a thrombus secondary to the inflammatory reaction. Right, Kodachrome of a more temporal and inferior view of the fundus showing more blotlike hemorrhages and abrupt vessel dilation characteristic of peripheral vessel occlusion.

tially the same intensity of inflammation. The left eye now had a funnel-shaped detachment of necrotic retina. Because the intensity of the reaction in the right eye had not decreased, the chlorambucil was discontinued and 100 mg of cyclophosphamide twice daily was started.

By Nov. 1, 1978, she had light perception only in the right eye. The anterior chamber on the right showed no change, and she had necrotic retinas with retinal detachments bilaterally (Fig. 6). The cyclophosphamide was stopped, her prednisone was tapered, and she continued taking the aspirin.

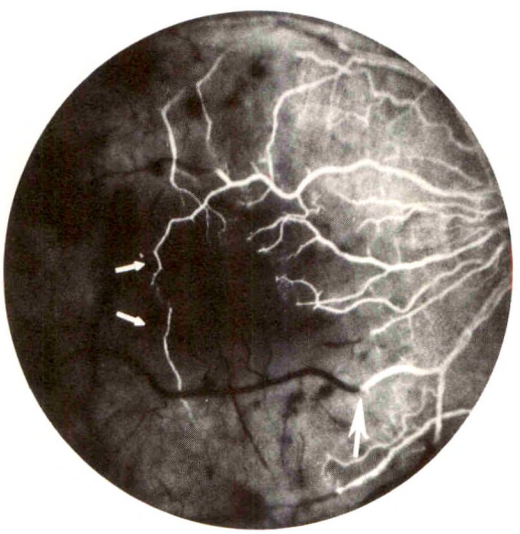

Fig. 5 (Price and Schlaegel). Fluorescein angiography shows the obliterative nature of this process. Compare the large arrow here to the one in Figure 4. The small arrows mark an arteriovenous anastomosis that has formed across the macula, apparently in response to the disease process; it was not present on the earlier fluorescein angiogram from Sept. 18, 1978 (Fig. 2).

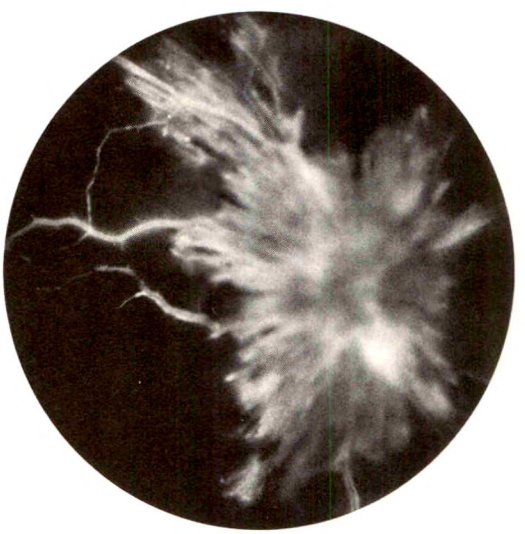

Fig. 6 (Price and Schlaegel). Fluorescein angiogram of the right eye on Nov. 1, 1978 shows diffuse leakage from the disk and from the few vessels that have remained patent.

Follow-up examination has shown a gradual decrease in her inflammatory process, but no other significant change.

Since first seen in the uveitis clinic, the patient was extensively examined for any systemic abnormality, but none was found. Despite the marked vasculitic changes in her retinas, neither neurologic or renal changes were noted during the entire time.

Erythrocyte sedimentation rates on Sept. 8, Oct. 5, and Nov. 8, 1978, were 12, 12, and 16 mm/hr, respectively. The purified protein derivative intermediate strength skin test was nonreactive, and that of streptokinase was 12.5 mm of induration. The VDRL test and fluorescent treponemal antibody-absorption was nonreactive. Enzyme-linked immunosorbent assays for *Toxocara* and *Ascaris* were negative, as were the rheumatoid latex agglutination. Antinuclear antibodies were not detected at a titer of 1:40. Her thyroxin level was normal at 10.1 μ/dl and her blood cell count showed a hemoglobin of 15.0 g/dl and a white blood cell count of 9,000/mm^3 with a differential of 1% bands, 52% polymorphonuclear cells, 43% lymphocytes, and 2% mononuclear cells. The indirect hemagglutination toxoplasmosis titer was 1:8. The cytomegalovirus titer of her serum was 1:32, but without change on repeat titers, and culture of the buffy coat for any viruses was negative. Her HLA profile was All, A24, B7, B15, and CW3. She was positive for W6 and negative for the other known A, B, and C antigens including B5.

Her blood was also checked for clotting abnormalities or evidence of any intravascular abnormalities, and results of the following tests were all within the normal limits: prothrombin time, 12.0 seconds; partial thromboplastin time, 22.5 seconds; fibrinogen, 280 mg/mm^3; thrombin time, 26.1 seconds; platelet aggregation with epinephrine, 95% at four minutes; platelet adhesiveness, 71%; antithrombin III, 42.8 mg/dl; duke bleeding time, one minute; C_3 compliment, 165 mg/dl; C_4 compliment, 39 mg/dl; cryoglobulins, negative; serum protein electrophoresis: albumin, 47.2%; alpha-$_1$, 4.8%; alpha-$_2$, 10.7%; beta, 13.5%; gamma, 23.8%. The serum immunoglobulins were increased with IgM, 2.50 mg/mm^3 (normal, 1.15± 0.26); IgA, 3.30 mg/mm^3 (normal, 1.69 ± 0.80); and IgG, 16.00 mg/mm^3 (normal, 9.76 ± 2.18). Her initial blood cell count on Sept. 8, 1978, showed some spherocytes and macrocytes, but these were not noted on subsequent testing.

On March 20, 1979, she still had visual acuity of light perception in the right eye and none in the left. Her applanation pressures were 0 mm Hg bilaterally. Ophthalmoscopic examination showed only a small area of viable retina in the superior periphery (Fig. 7).

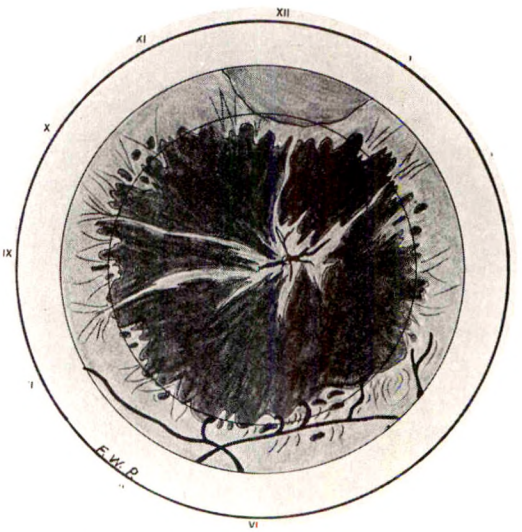

Fig. 7 (Price and Schlaegel). Fundus drawing of the right eye March 20, 1979. The posterior pole is now bare retinal pigment epithelium with only a few strands of white retina over it. Superiorly there is a small area of attached retina. The rest of the peripheral retina is detached and atrophic. Inferiorly, there are some large vessels that originate anteriorly. Vitreous haze is nearly gone at this point.

Discussion

Our case appears to be another example of bilateral acute retinal necrosis as reported by Young and Bird.[1] The disease process here is similar, although our patient's age of 21 years is much younger than their four cases ranging from 57 to 63 years of age. Willerson, Aaberg, and Reeser[2] also reported two cases of a fulminant retinal vaso-occlusive disease that destroyed the retina bilaterally in each patient just as in our case (their patients were 65 and 30 years of age). One of their patients displayed systemic manifestations of Behçet's disease including aphthous ulcers and iridocyclitis with hypopyon. Their second patient had iridocyclitis and a history of vulvar sores.

Willerson's first patient was treated with isoniazid, chlorambucil, and prednisone. Although it was suggested that antimetabolite treatment may have led to a quiescence of the retinal vasculitis, one eye progressed from an apparently minimally involved state to a diffuse vasculitis of the retina on this treatment. The sec-

ond patient was treated with corticosteroids topically, subconjunctivally, and orally, as well as with pooled transfer factor, none of which changed the course of her disease. All four of these eyes apparently ended with visual acuity of light perception at best.

Young and Bird,[1] however, only treated their four patients with corticosteroids (two also were treated with an antibiotic). Four of these eight eyes retained visual acuity of 6/12 (20/40) to 6/60 (20/200). The one woman in their study was the only patient to end up with bilateral blindness, but even her vasculitis may have decreased on the corticosteroid treatment. However, they suggested that treatment did not appear to alter the course of the disease. Whether it did, or whether their patients did not manifest the extent of the disease as in our patient and Willerson's is unknown.

The end result in all of these cases appears to be a vitreous contraction from the inflammatory process with traction on the necrotic retina causing either or both a traction retinal detachment and a rhegmatogenous retinal detachment. These detachments sometimes occurred after the inflammation had resolved and they invariably proved to be impossible to repair if attempted.

As previously noted, our patient showed no decrease in her vasculitis with corticosteroids or chlorambucil, although she was not given the full dose of 20 mg per day as sometimes used by Mamo.[5] It is interesting in our case that such a severe vasculitis of the retina could develop without any hematologic changes suggestive of a more diffuse vasculitis in the body or neurologic changes suggestive of a vasculitis in the central nervous system. Only one of the previously reported cases gives any evidence of systemic involvement[2] and two others had increased sedimentation rates with one of these having evidence of ankylosing spondylitis on x-rays.[1]

Whatever the causal agent, it would appear to be specific for the retina with some involvement and inflammation of the uveal tract as well. All cases, except one, appear to have been in patients with an apparently normal immunologic status before treatment.

Evidence for Behcet's disease in our patient is circumstantial at best. Her retinal changes with obliterative vasculitis and low-grade fever during her beginning attack are consistent with those described by Mamo and Baghdassarian.[6] Emotional stress, chronic sore throats for one year before onset, and being in the 20- to 30-year age group are also noted to be associated with Behçet's disease.[6] However, our patient lacked the other more common signs and symptoms of Behçet's disease needed to make a diagnosis.

Herpes virus infections have been noted to have a similar appearance to bilateral acute retinal necrosis,[7,8] but such cases seldom occur beyond infancy. The possibility of herpes and cytomegalovirus infections as the cause of bilateral acute retinal necrosis were discussed at length in the previously mentioned reports. However, we cannot attribute a firm diagnosis of this condition to any virus.

The terminology that has developed in published reports regarding these cases is potentially confusing. We have chosen the terminology used by Young and Bird,[1] bilateral acute retinal necrosis, because it aptly describes the overall nature of these reported cases, stresses the devastating potential of the process, and supplies an easily remembered acronym. (BARN). Willerson, Aaberg, and Reeser[2] chose necrotizing vaso-occlusive retinitis which describes the local vascular reaction. Finally, Bloom and associates[9] have recently described three cases of acute retinal necrosis that were secondary to

blunt trauma, had no vaso-occlusive component, and were self-limiting processes without the marked inflammation and vitreous contraction present in the cases discussed here.

Summary

A 20-year-old woman lost all useful vision over a 2½-month period as a result of a necrotizing and occlusive vasculitis of the retina. Treatment with prednisone, immunosuppressants, and aspirin was unsuccessful. No systemic manifestations of the disease were found and no cause was discovered.

Kodachromes and fluorescein angiograms showed the progression in one eye from normal to near total retinal necrosis. The process began with a mild venous dilation and peripheral arteritis that progressed into an obliterative vasculitis with abrupt vessel dilation, hemorrhages, and retinal swelling. This was followed by necrosis and sloughing of the retina into the vitreous. Vitreous contraction and necrotic retina produced unrepairable retinal detachments.

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ABNORMALITIES OF THE PUPIL AND VISUAL-EVOKED POTENTIAL IN QUININE AMBLYOPIA

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Quinine has been effective in the management of leg cramps, myotonia congenita, resistant *Plasmodium falciparum*, and eyelid myokymia. The first description of ocular toxicity dates back to 1841 when Giacomini[1] described a case of quinine amblyopia. Quinine toxicity occurs in one out of 100,000 persons susceptible to this drug.[2] An idiosyncratic sensitivity is the probable mechanism of a toxic response to small amounts of quinine. The average dose of quinine is 5 to 10 grains with daily dosages not exceeding 33 grains. Toxic visual symptoms have been reported from dosages as low as 1.0 grain.[2]

In mild toxic reactions, symptoms consist of slight clouding or flickering of vision, noises in the ears, weakness, and confusion. In more severe cases, there is sudden complete blindness, dizziness, tinnitus, and partial deafness. Loss of vision may not occur for days or weeks.[2] The most severe cases develop deep coma with circulatory collapse, followed by complete blindness, first evident when consciousness returns. As a rule, central vision recovers, at least partially, with constriction of the peripheral fields remaining permanently. Other disorders noted in quinine toxicity include disturbed color perception, photophobia, diplopia, night blindness, scotomas, mydriasis with poorly reactive pupils, and iris atrophy.[3]

Investigation into the mechanism of ocular involvement has failed to establish whether quinine exerts its deleterious action through a primary injury to the ganglion cells and nerve fibers or secondarily through vascular changes in the retina. Emphasis has often been directed to the severe constriction of the retinal arterial system in cases of intoxication. Retinal ischemia, retinal edema, and optic disk pallor have been noted. Perhaps a combination of both vascular and neural elements are involved in the development of the toxic reaction.[4]

Many cases of quinine ocular toxicity have been reported where electroretinographic, electro-oculographic, and pupillary studies have been performed. To the best of our knowledge, there have been no published reports of the measurement of the visual-evoked potentials or mention of a transient tonic pupillary response with denervation supersensitivity in a patient with quinine ocular toxicity. We describe a patient who developed bilateral blindness, transient tonic pupils with denervation supersensitivity and iris atrophy, and abnormal visual-evoked potentials in addition to other characteristic findings seen in quinine toxicity. Quinine sulfate is still used in the general medical community for the treatment of leg cramps. Ophthalmologists should consider quinine toxicity in any patient with sudden onset of bilateral blindness and poorly reactive pupils.

CASE REPORT

A 54-year-old man was given 5 grains of quinine sulfate tablets for treatment of lower ex-

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tremity muscle cramps. The patient took one tablet, three times daily for eight days, and then discontinued them. Three days after he stopped taking the quinine sulfate, the patient developed nausea, vomiting, and a headache in the evening. On awakening the next day, the patient discovered he was blind. The patient was seen at Martinez V.A. Hospital and was admitted to the neurology service.

Ophthalmoscopic examination on the day of admission showed a visual acuity of no light perception in both eyes; pupils that were equal at 5 mm and unreactive to light; and normal results from slit-lamp and ophthalmoscopic examinations. Pertinent laboratory findings included the following: a normal brain scan, normal computed tomography scan, normal serology, normal blood chemistry except for blood urea nitrogen of 30 mg/100 ml, and a sedimentation rate of 52 mm. Neurologic examination was unremarkable and the patient was believed to have quinine amblyopia. He was given 60 mg of prednisone daily, and 40 mg of hydralazine daily, which was discontinued after three days at the recommendation of a consulting ophthalmologist because there was no improvement. Six days after admission, the patient's visual acuity improved to light perception; his pupils were oblong, which was suggestive of ciliary muscle ischemia; and ophthalmoscopic examination showed diffuse anteriolar spasm. Fifteen days after admission, the patient's visual acuity was corrected to 6/6 (20/20), in both eyes, his pupils had a trace reaction to light, and slight pallor of both optic disks was noted. After approximately 1½ months of hospitalization, during which time the patient also underwent a cholecystectomy secondary to cholelithiasis, he was discharged.

Follow-up ocular examinations were performed here from the time of discharge until one year after the toxic quinine reaction. During this period, the patient maintained a best corrected visual acuity of 6/6 (20/20) in both eyes, and was noted to have a red/green and blue/yellow color deficit, bilateral optic atrophy with pigment mottling and thinning of the retinal pigment epithelium in the posterior pole, and narrowing of the arterioles and veins with a mottled choroidal filling pattern on fluorescein angiography.

Seven months after the onset of quinine toxicity, examination revealed oblong pupils (Fig. 1) that reacted only a trace amount to light but moderately to an accommodative target with a tonic response. On follow-up examination ten months after the onset of symptoms, the pupillary response had improved to a moderate reaction to light with no further tonic response to an accommodative target. Iris atrophy was present in both eyes on slit-lamp examination. Cocaine, 10.0%, was administered to the right eye followed by the pupil dilating from 3 to 6 mm over a one-hour period. Pilocarpine 1/16% was administered to the left eye; the pupil constricted from 5 to 2 mm over a one-hour period, which indicated denervation supersensitivity (Fig. 2). Luneau anesthesiometer readings found corneal sensitivity to be normal. The cocaine and pilocarpine tests were performed ten months after the onset of symptoms. Normal dilation of the pupils to mydriatics was noted.

Visual field examinations were performed one year later and showed constriction of the patient's fields in both eyes (Fig. 3). Electroretinogram (ERG), electro-oculogram (EOG), and visual-evoked

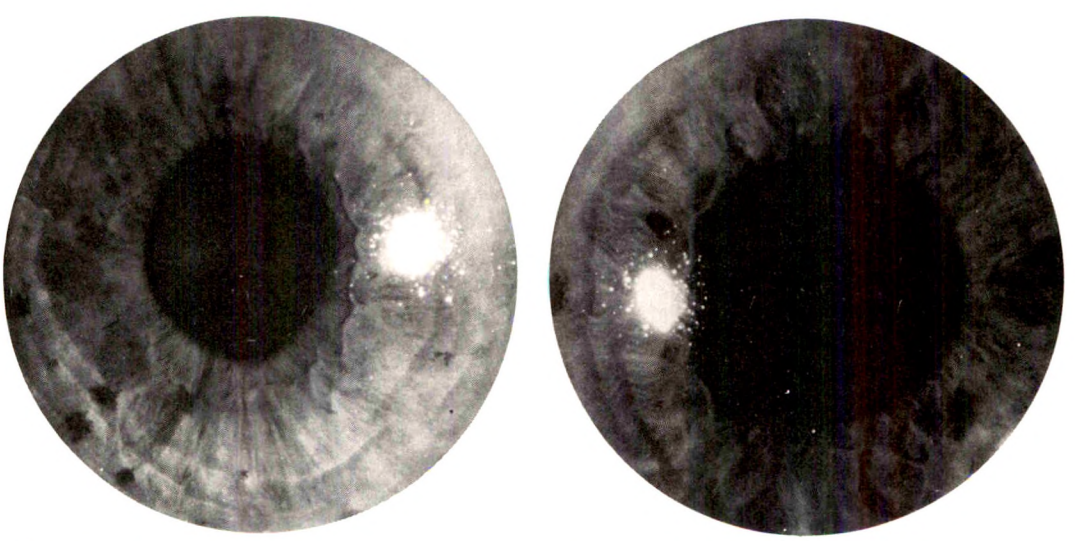

Fig. 1 (Gangitano and Keltner). Note pupil irregularity in both right (left) and left (right) eyes.

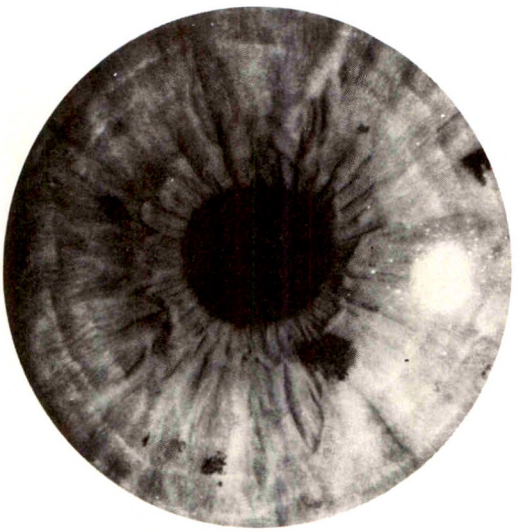

Fig. 2 (Gangitano and Keltner). Note pupillary constriction in the left eye one hour after pilocarpine 1/16%.

potentials to pattern shift and bright flash were performed four months after the patient's episode of quinine-induced amblyopia. The ERG was recorded according to standard techniques using Burian-Allen contact electrodes.[5] The ERG revealed a flat photopic response and scotopic responses showed a deep a-wave with an absent b-wave. A poor flicker response was noted at 20 flashes per second (Fig. 4). The EOG was recorded according to standard techniques and was normal,[5] with a light peak to dark trough ratio in the right eye of 3.0 and in the left eye of 3.3.

Visual-evoked potentials were recorded using gold-plated disk electrodes placed according to the International 10-20 Electrode System. The visual-evoked potentials were recorded over the left (O_1) and right (O_2) hemispheres and referenced to left mastoid (A_1) and right mastoid (A_2), respectively. A 30-minute pattern reversal at two reversals per second and bright flash stimulus were used for the visual-evoked potential recordings. The visual-evoked potentials were abnormal in both eyes regarding waveform and latency. The pattern shift of visual-evoked potentials in the right eye was flat despite a corrected visual acuity of 6/6 (20/20) (Fig. 5). The pattern shift in the left eye showed a prolonged latency.

Bright flash visual-evoked potentials showed marked distortion of the waveform in both eyes (Fig. 6).

Discussion

In some patients, toxic reactions are manifested only by central nervous system depression in the form of drowsiness or sleep. Many patients awake the next day and find themselves blind, as in our patient. Our case is similar to other cases in which the optic nerve, retina, and retinal vessels were normal when the patient was first seen; then optic atrophy and

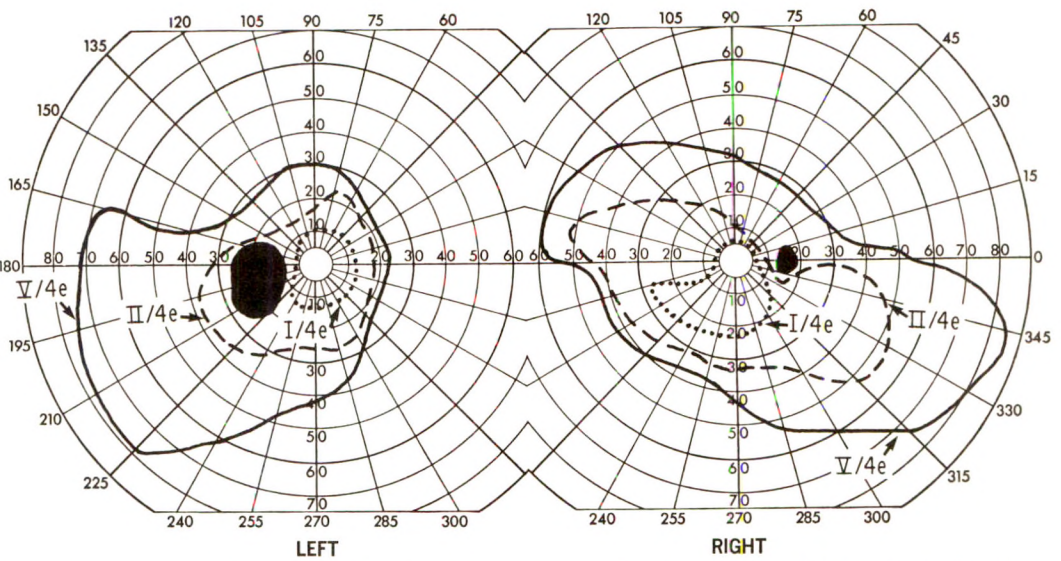

Fig. 3 (Gangitano and Keltner). Goldmann fields are constricted and irregularly depressed in both eyes.

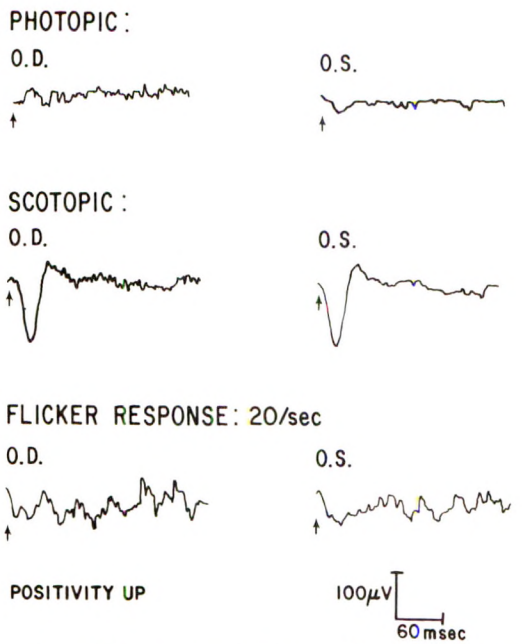

Fig. 4 (Gangitano and Keltner). Electroretinogram and flicker response.

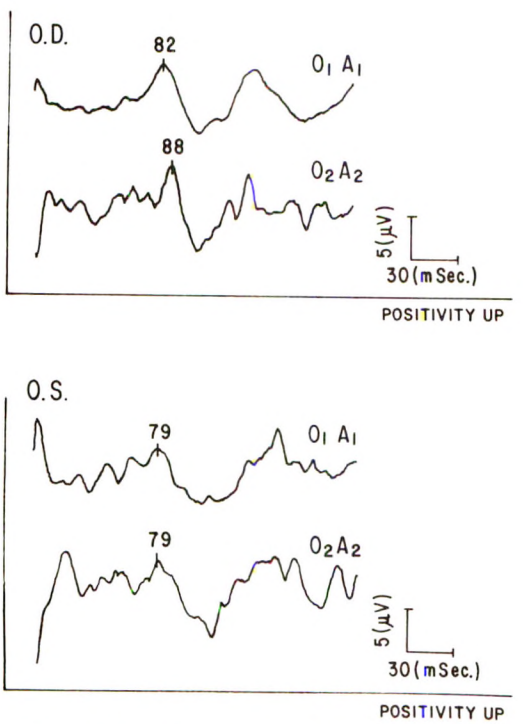

Fig. 6 (Gangitano and Keltner). Bright flash visual-evoked potentials show marked distortion of waveform in both eyes.

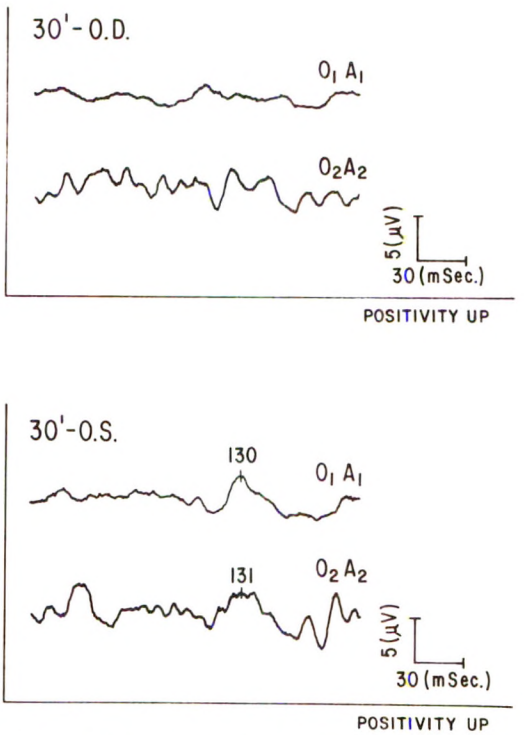

Fig. 5 (Gangitano and Keltner). Visual-evoked potentials to pattern shift show flat response in the right eye (top) with marked prolongation of latency in the left eye (bottom).

attenuation of vessels appeared days to weeks later.[6] In patients who have suffered toxic reactions to quinine, pathologic studies have shown degeneration of the retinal ganglion cells and nerve fibers with atrophy of the rods and cones.[3]

The usual visual field change in quinine toxicity is one of concentric contraction. Frequently, the contraction of the visual field is greatest in the vertical meridian.[2] Improvement of the visual fields may take days or months after the initial toxic insult with central vision improving first and some degree of contraction remaining permanently. Changes in visual field and visual acuity are accompanied by changes in electrophysiologic measurements.

The ERG remains almost normal during the initial marked loss of vision, but becomes definitely abnormal during

the beginning phase of visual improvement. Depression of the ERG and disappearance of the b-wave have been noted.[3,7] In our case, there was an abnormal photopic and scotopic response manifested by an essentially absent b-wave. It has been suggested that the ERG findings might be explained by the effects of quinine on retinal elements at the bipolar cell level rather than the rods and cones. The ERG in this patient would certainly support that contention because his a-wave is normal under scotopic conditions with a totally absent b-wave. However, the poor flicker response and absent photopic ERG would suggest probable cone dysfunction. These findings indicate that probably both the photoreceptors and bipolar layers were involved. After the third week following the onset of quinine toxicity, it is believed that the ERG changes are definitive and will not change further, whatever the visual acuity may be.[8]

Changes in the EOG parallel changes in the visual acuity,[7] showing an absent light response during the initial acute loss of vision, but subsequently returning gradually to normal as vision improves. In later stages, when the visual fields remain constricted and the ERG is abnormal, the EOG may be back to normal, as in this case.[3]

To the best of our knowledge, there have been no published reports of the effect of quinine toxicity on the visual-evoked potentials. In our case, visual-evoked potentials were performed both to pattern shift and bright flash. The right eye to 30 minute check size pattern showed no reproducible visual-evoked potentials despite a corrected visual acuity of 6/6 (20/20) in that eye. The left eye showed a prolonged positive wave at 130 msec. Bright flash visual-evoked potentials showed an early positive peak but a distorted waveform in both eyes. Thus, the visual-evoked potentials were abnormal in both eyes regarding waveform and latency, and this suggests a conduction abnormality in the nerve fiber layer and optic nerve.

In our case, the pupils were initially unreactive to light and accommodation. Over a period of ten months, the pupils improved to a moderate reaction to light. Pupillary reaction to a near accommodative target was noted early to be moderate with a tonic response. Examination ten months after the quinine insult revealed the pupillary response was normal to a near accommodative target. Denervation supersensitivity was noted by a marked pupillary constriction after the administration of 1/16% pilocarpine. It has been reported that after recovery of vision, pupils remain dilated with a poor reaction to light, or that pupils were dilated and reacted to convergence but not to light.[9] We could find no mention of a transient tonic pupillary response or supersensitivity to weak cholinergics in published reports. This previously unreported finding of a tonic pupil with a positive supersensitivity reaction is probably secondary to iris, ciliary body, or ciliary ganglion ischemia. The oblong pupils are also probably secondary to ischemia of the iris and ciliary body. Normal dilation of the pupils to cocaine and mydriatics was noted.

The problem of therapy in quinine amblyopia is unresolved. All therapeutic attempts have been based on the assumption that retinal vascular insufficiency is of some importance in the pathogenesis of retinal toxicity.[6] A great number of drugs intended to promote dilation of the retinal vessels have been tried, but without conclusive evidence of benefit. Because the prognosis for recovery of useful vision is good, it has been difficult to evaluate clinically what value vasodilators might have in the treatment of quinine toxicity.

Summary

Total blindness with a transient tonic pupillary response, denervation supersensitivity, and abnormal visual-evoked

potentials developed in a 54-year-old man after the use of quinine sulfate for leg cramps. He later recovered normal visual acuity. A transient tonic pupillary response, denervation supersensitivity, and abnormal visual-evoked potentials in quinine toxicity, to our knowledge, have not been previously reported.

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OPTIC NEURITIS AND SYSTEMIC LYMPHOMA

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In contrast to leukemia, systemic nodal lymphoma rarely involves the eyes or the optic nerve; it is more likely to involve the orbit. Poorly differentiated lymphomas represent up to 10% of all malignant neoplasms of the orbit.[1] Ocular involvement by reticulum cell sarcoma, although uncommon, has been described extensively in published reports. It is probably the most frequent intraocular lymphoma. Retinal and vitreous infiltration by reticulum cells often develop, producing a nonspecific uveitis.[2–11] Patients with Hodgkin's lymphoma, however, only occasionally have uveal tract or retinal involvement.[12–14] Likewise, optic nerve involvement by any form of lymphoma is rare; both reticulum cell sarcoma and Hodgkin's lymphoma have been implicated.[15–20] Primary intracranial origin was postulated in some cases,[15–28] whereas in others optic nerve infiltration developed as a complication of leptomeningeal lymphomatosis or orbital metastatic lymphoma.[19–22]

We describe one patient who developed an optic neuritis as the initial manifestation of leptomeningeal infiltration by a poorly differentiated lymphocytic lymphoma. Analysis of the cerebrospinal fluid revealed a lymphocytic cellular reaction alternating with neoplastic cells; classification of these lymphocytes further defined the tumor as a thymus-cell lymphoma (T-cell or malignant lymphoma, lymphoblastic); treatment resulted in rapid, long-lasting improvement. We emphasize the increasing frequency of leptomeningeal lymphomatosis, a late complication of systemic lymphoma that can be seen in association with visual and oculomotor disturbances.[20,21] Combined radiotherapy and intrathechal chemotherapy can frequently arrest tumor growth in the meninges.[23]

CASE REPORT

A 26-year-old man came here in October 1977 because of a two-week history of rapidly progressive, painful visual loss in the right eye. The patient had been seen elsewhere four months earlier because of shortness of breath. Examination at that time showed a left pleural effusion and left supraclavicular lymphadenopathy. Biopsy of the enlarged lymph node established a diagnosis of diffuse, poorly differentiated lymphocytic lymphoma. Subsequently, an abdominal lymphangiogram showed enlargement of retroperitoneal lymph nodes. Bone marrow biopsy and aspirate were negative for tumor involvement, and the tumor was thus classified as probably stage IV lymphoma. Treatment with a combination regimen of cyclophosphamide, vincristine, and prednisone resulted in significant improvement. At the onset of visual symptoms the patient was receiving the fifth monthly chemotherapeutic cycle.

On admission, visual acuity was R.E.; light perception and L.E.: 6/6 (20/20). The patient was able to read all the Ishihara color plates with the left eye and could not identify red color light with the right eye. Visual fields tested in the Goldmann perimeter were normal in the left eye and showed light perception in the inferonasal field of the right eye. The right pupil measured 6 mm and reacted sluggishly to direct light; the left pupil measured 2 mm and disclosed normal reaction to light and accommodation. A normal consensual pupillary photomotor response was found in the right eye and a swinging flashlight test showed the presence of an afferent pupillary defect in the right eye. No proptosis was noted and results of the oculomotor examination were normal. Slit-lamp examination disclosed a normal anterior segment without evidence of inflammatory reaction in the vitreous in either eye.

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Applanation pressures were 18 mm Hg in both eyes. Examination of the right fundus showed swelling of the optic nerve head, blurred disk margins and absence of spontaneous venous pulsations. Additionally, small peripapillary flame-shaped hemorrhages were observed. The remaining posterior pole and retina were normal. Examination of the left fundus showed swelling of the supernasal disk margin as the only abnormality and was otherwise unremarkable.

Neurologic examination showed a normal mental status; no signs of meningeal irritation were present. Results of cranial nerve examination with the exception of the above described findings were normal. The patient had a motor peripheral neuropathy without evidence of lateralizing motor signs of pathologic reflexes.

Results of roentgenologic examination of the skull and the optic foramina were normal. Hypocycloidal tomograms of the optic canals in both anteroposterior and the submentovertex views were normal. Unenhanced and contrast enhanced computed tomography scan of the brain and orbit were normal. Results of routine blood tests were normal, and a spinal tap showed slightly xanthochromic cerebrospinal fluid under normal pressure. Cytochemical analysis showed the following: 720 white blood cells, 90% of them lymphocytes; 80% of these lymphocytes were identified as T-lymphocytes by using sheep red-cell rosette formation patterns and surface immunoglobulin markers. Further examination of the cerebrospinal fluid showed occasional neoplastic cells alternating with normal appearing lymphocytes. Gram stain and India ink preparations were negative. No growth of bacteria, tubercle bacillus, or fungi was observed. Repeat bone marrow biopsy and aspirate showed no evidence of tumor.

The patient was treated with prednisone daily, combined with cyclophosphamide, doxorubicin, and vincristine. Additionally, 15 mg of intrathecal methotrexate was given biweekly for two months. Radiation therapy was begun the morning after admission and was extended for ten consecutive days. A total dose of 3,220 rads was delivered to the brain and the craniospinal axis down to the level of C_2 to C_3. Orbital contents were shielded as is usually done in cranial irradiation.

Forty-eight hours after admission and one dose of intrathecal methotrexate, initiation of radiation therapy, and a total dose of 120 mg of prednisone orally, the patient described significant visual improvement. Ophthalmologic examination disclosed a visual acuity of L.E.: 6/6 (20/20) and R.E.: 6/12 (20/40). The patient was able to identify the first number of the Ishihara color plates and visual field examination in the Goldmann perimeter showed an absolute scotoma to red and a relative central scotoma to an I_2 isopter in the right visual field. Results of the remainder of the ophthalmologic examination were unchanged. Fluorescein angiogram showed leakage of the dye in the optic nerve head of the right eye (Fig. 1) and was normal in the left eye. One week after initiation of treatment, the visual fields were normal, and the scotoma to red target previously found had disappeared. A right afferent pupillary defect remained and the ophthalmoscopic examination showed considerable lessening of the disk edema and resolution of the peripapillary hemorrhages in the right eye (Fig. 2); the left eye was normal.

In early May 1978, the patient developed bilateral pleural and pericardial effusions. Peripheral blood smear and bone marrow aspirate now showed an appearance of lymphocytic leukemia. Results of neuro-ophthalmologic examination on this occasion were normal and a lumbar puncture showed normal

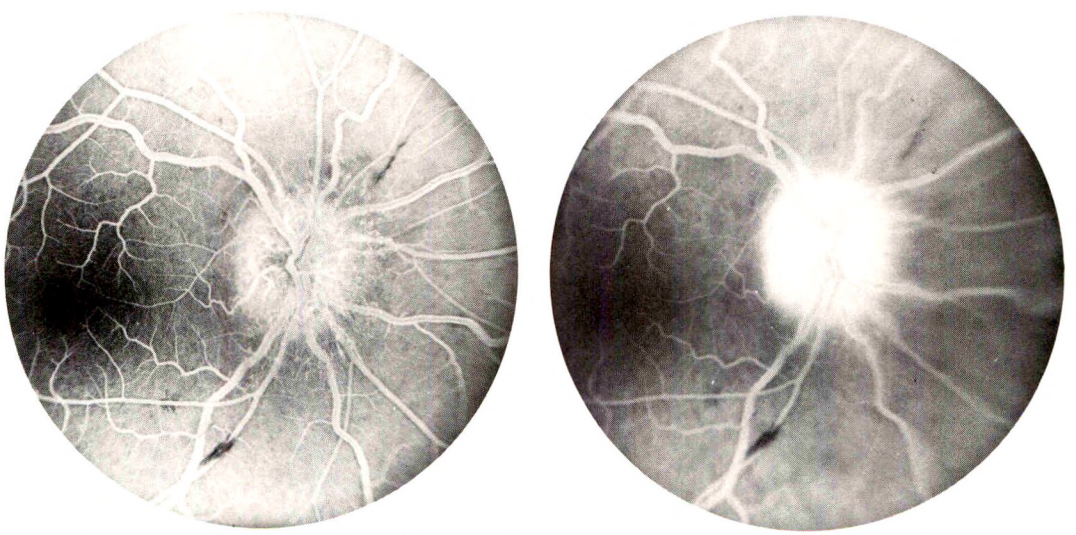

Fig. 1 (Kattah and associates). Left, Fluorescein angiogram of right eye in arteriovenous phase showing dilated capillaries on the optic nerve head and leakage of fluorescein. Right, Persistent staining of nerve head and leakage of fluorescein during late phase of the same angiogram.

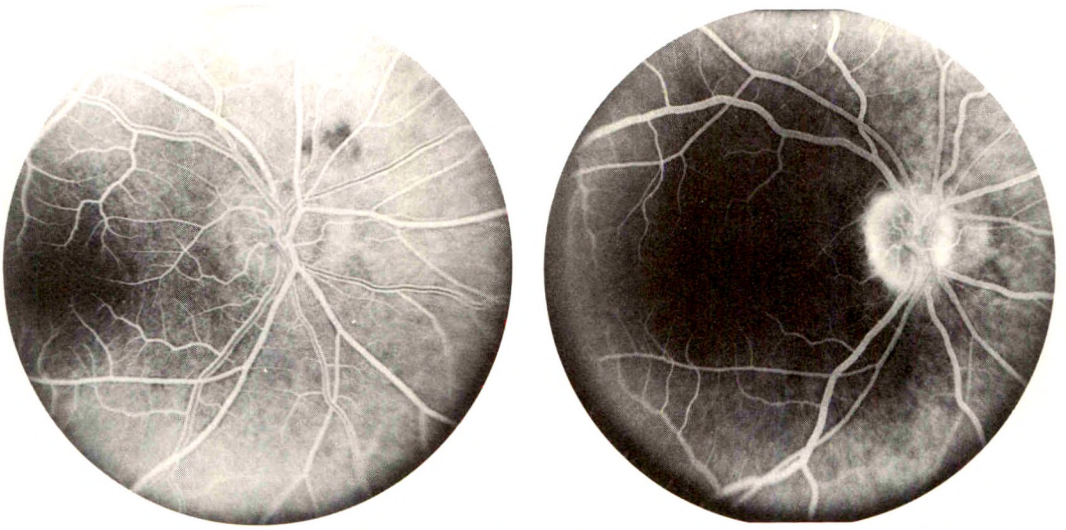

Fig. 2 (Kattah and associates). Arteriovenous (left) and late phase (right) angiograms of patient's right eye approximately one month after initial manifestation. Dilated optic nerve head capillaries and fluorescein leakage are no longer present.

cerebrospinal fluid. The initial pulmonary involvement seen in this patient and the subsequent lymphocytic leukemic transformation, in addition to the high percentage of T-cell lymphocytes in the cerebrospinal fluid, established the diagnosis of lymphoblastic-lymphoma, and the patient was given chemotherapy with L-asparaginase, vincristine, and prednisone orally. Six weeks later he had recurrence of the pleural and pericardial effusions, hepatosplenomegaly, and hepatic failure. He was treated with high-dose methotrexate. The patient developed sepsis and bleeding secondary to massive bone marrow infiltration; two days later he lapsed into a coma and died. Permission for autopsy was not granted.

Discussion

Although malignant lymphomas are essentially a systemic disease, in most cases the tumor begins as a focal proliferation of lymphocytes in lymph nodes or an extranodal site. This ocular, orbital, and optic nerve involvement by lymphoma in some cases precedes systemic disease,[2–10,12] whereas in others it represents a complication of generalized lymphoma.[18,19] Ocular involvement by reticulum cell sarcoma (malignant histiocytic lymphoma) is well known.[2–11] Patients with this form of ocular lymphoma develop a nonspecific uveitis that is often resistant to therapy and indistinguishable from intractable uveitis of other causes. Multifocal chorioretinal infiltrates can be found on ophthalmoscopic examination when the severity of the vitreous reaction does not preclude visualization of the fundus.[2–11] Vitrectomy may establish an early diagnosis and result in improvement of vision in some cases.[8] Histologically, multiple foci of malignant lymphomatous tissue can be found scattered in the retina, choroid, and vitreous.[2–11] Ocular involvement of reticulum cells often precedes central nervous system or systemic lymphoma by months or years.[3–6] One of the features of this neoplasm when it involves the central nervous sytem is the potential for cure or palliation with radiotherapy; complete remission of the tumor has been accomplished in several cases, which stresses the need for an early diagnosis.[25,26] The appearance of leptomeningeal lymphomatosis as observed in our case is uncommon with reticulum cell sarcoma. On the contrary, large tumor masses in the cerebral hemispheres, cerebellum, and brainstem are frequently found.[27] Ocular

infiltration by Hodgkin's lymphoma is by far less common than ocular reticulum cell sarcoma. Primbs, Monsees, and Irvine[12] described one patient who developed a uveitis 18 months preceding systemic involvement by Hodgkin's lymphoma; the patient subsequently died and histopathologic examination of the eyes disclosed vitreous and retinal infiltration by well differentiated lymphoma and Sternberg-Reed cells. Infiltrative retinopathy in patients with Hodgkin's lymphoma has been described also.[13,14]

Visual loss as a result of an optic neuropathy in patients with different types of lymphoma is infrequent. Among 5,778 patients with lymphoma reviewed by Williams and associates,[22] only one case with optic nerve involvement was found. Optic neuritis probably results from tumor invasion of the meningeal sheath of the optic nerve with subsequent compression or infiltration of the nerve.[21] Primary Hodgkin's type lymphoma of the central nervous system has been described as occurring with optic neuropathy and a chiasmal syndrome in two different instances[17,18]; diagnosis in these cases was made by autopsy or biopsy specimen examination. Primary malignant lymphomas of the central nervous system of the reticulum cell sarcoma type have been reported also in cases that initially developed an optic neuropathy in the context of rapidly progressive neurologic deterioration leading eventually to death; diagnosis was established at autopsy.[15,16] The presence of optic neuropathy in patients with generalized systemic lymphoma as a component of neoplastic leptomeningeal infiltration is also uncommon and far less frequent than carcinomatous optic neuritis. None of the patients with leptomeningeal lymphomatous described by Griffin and associates[23] and only one of 13 patients described by Bunn and associates[24] had optic nerve involvement. Lymphoma located in the orbital apex can produce optic nerve and oculomotor compression or infiltration resulting in visual loss associated with ophthalmoplegia.[21] Considering the high incidence of central nervous system infections in patients with lymphoma[28] and the possibility of infectious optic neuropathy,[29] the differential diagnosis of optic neuritis in patients with lymphoma includes herpes zoster,[30] *Cryptococcus*,[31] *Toxoplasma, Candida,* and the like. The neurotoxic effects of radiation or chemotherapy, or both, should also be studied. Sanderson, Kwabara, and Cogan[33] implicated vincristine toxicity as a possible cause for an otherwise unexplained optic neuropathy in a patient with lymphoma. Fishman, Bean, and Cogan[34] reported one case of optic atrophy after chemotherapy and cranial radiation in a patient with acute lymphocytic leukemia.

With aggressive chemotherapy, prolonged disease-free survival has been described in patients with diffuse histiocytic lymphoma.[35] This is apparently associated with an increased incidence of leptomeningeal lymphomatosis[24]; the primary clinical manifestations of lymphomatous meningitis include cranial nerve palsies and changes in mental status associated with a subacute meningeal syndrome.[36] Invasion of the leptomeninges by systemic lymphoma is probably the result of direct extension from adjacent involved bone via perforating dural vessels.[24] In most cases reported by Griffin and associates[23] with leptomeningeal lymphomatosis, evidence of bone marrow involvement was found at autopsy. In contrast, we were unable to show lymphomatous invasion in the first bone marrow aspirate examined.

Leptomeningeal invasion by lymphoma is associated with increased protein and decreased glucose in the cerebrospinal fluid. Identification of neoplastic cells can be accomplished in most cases.[23] Additionally, a benign lymphocytic cellular

reaction is usually seen. T-cells were identified in the cerebrospinal fluid in our patient with characteristic rosette formation and lack of surface immunoglobulins; thus, leading to a probable diagnosis of thymus-cell lymphoma.[37] Although no systematic study of cytologic characteristics of lymphocytes in cerebrospinal fluid is available and the significance of this finding has not yet been determined, the clinical course in our case is characteristic for T-cell lymphoma.

Thymus-cell lymphoma or malignant lymphoma, lymphoblastic as described by Nathwani, Kim, and Rappaport,[38] is an infrequent tumor occurring in children and young adolescents that has some of the hematologic and clinical features of acute lymphocytic leukemia and shares with it a common origin from T-cell derived lymphocytes.[39] The neoplasm frequently begins as a mediastinal mass and is complicated with late bone marrow involvement resembling that of classic acute lymphocytic leukemia. The prognosis in general is poor with involvement of the central nervous system being found almost invariably.[38] Among 450 non-Hodgkin's lymphomas reviewed by Nathawani, Kim, and Rappaport,[38] 14 were classified as T-cell lymphomas. Other lymphomas possibly originating from abnormalities in the T-cell system regulation include Hodgkin's disease, mycosis fungoides, and the Sezary syndrome.[40] With the advancement in the immunologic classification of lymphomas, a better understanding of the biologic behavior of these tumors will lead to their classification and treatment.

Summary

A 26-year-old man with stage IV poorly differentiated lymphocytic lymphoma complained of visual loss of two weeks' duration. Examination revealed visual acuity of light perception in the right eye secondary to optic neuritis and other tests revealed the presence of lymphomatous leptomeningeal infiltration. Combined treatment with intrathecal methotrexate, prednisone, and whole brain radiation resulted in rapid long-lasting recovery of visual functionof the right eye. The cerebrospinal fluid contained a large amount of thymus-derived lymphocytes and the subsequent clinical course observed with characteristic of T-cell or malignant lymphoblastic lymphoma.

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MEDULLOBLASTOMA CAUSING A CORTICOSTEROID-RESPONSIVE OPTIC NEUROPATHY

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The sudden onset of unilateral visual loss together with signs of optic-nerve dysfunction in a patient in the age range of 15 to 45 years usually suggests a diagnosis of optic neuritis. In such cases, improvement in visual function after administration of systemic corticosteroids is believed to support this diagnosis.

We encountered a case in which a presumed optic neuritis responded completely to corticosteroid therapy but recurred whenever corticosteroids were withdrawn. After neurologic signs and symptoms appeared, the patient was reexamined and was found to have a medulloblastoma causing optic nerve compression. To the best of our knowledge this is the first reported case in which direct compression of the optic nerve has occurred as a result of extension of a posterior-fossa medulloblastoma.

CASE REPORT

A 25-year-old man had a history of decreased vision in the right eye of eight weeks' duration. Visual acuity was R.E.: 6/15 (20/50) with a central scotoma, and L.E.: 6/6 (20/20). The right optic disk was mildly edematous. A diagnosis of papillitis was made, and the patient was given 40 mg of prednisone orally on alternate days. Rapid improvement in visual acuity occurred within two weeks. The corticosteroids were subsequently tapered; however, the patient then began to have diffuse headache. He also complained of balance difficulties and occasional low-back pains that radiated into the left foot. Computed tomographic scan showed an ill-defined density occupying the vermis cerebelli (Fig. 1) with forward displacement of the fourth ventricle. Contrast computed tomographic scan showed minimal enhancement of this mass. The patient was then referred to us for further examination.

On admission the findings of a neurologic and general examination were within normal limits. On neuro-ophthalmologic examination, the patient's visual acuity was 6/6 (20/20) in the right eye with difficulty at distance and near, and he could identify only four out of ten H-R-R color plates. Visual acuity in the left eye was 6/6 (20/20) at distance and near, and he could identify all of the color plates with that eye. There was no afferent pupillary defect of the right eye, but the visual field in that eye had an irregular inferior defect (Fig. 2). The left visual field was normal. The rest of the results of the examination were normal except for a minimal hyperemia and blurring of the right optic disk. A repeat com-

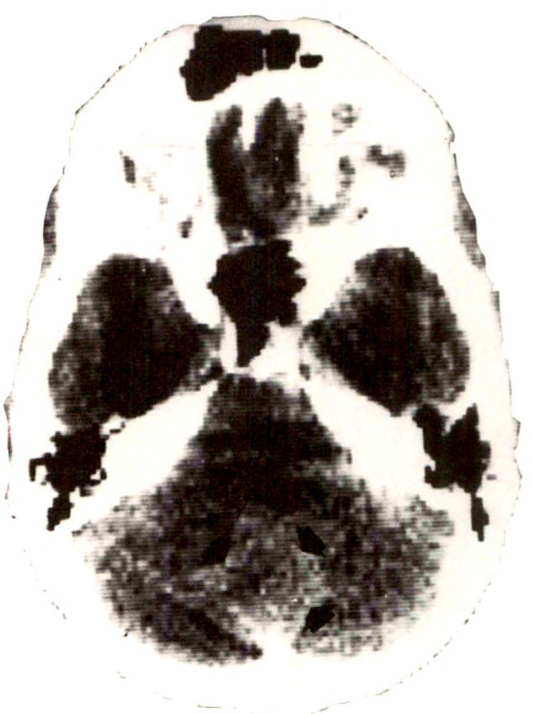

Fig. 1 (Hirst and associates). Noncontrast computed tomographic scan with vermian mass (black arrows) with forward displacement of fourth ventricle (open arrows).

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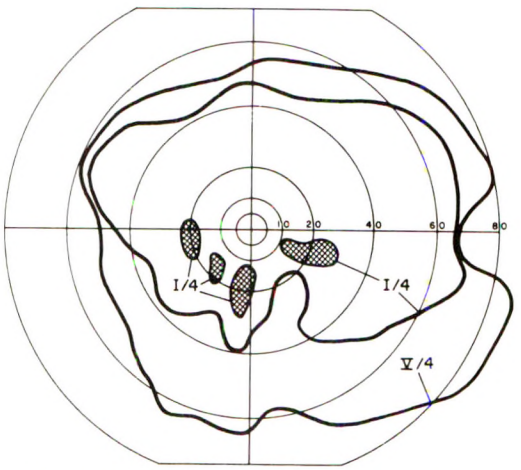

Fig. 2 (Hirst and associates). Visual field, right eye, with irregular inferior field defect and relative scotomas.

Fig. 3 (Hirst and associates). Noncontrast computed tomographic scan showing dense suprasellar mass (black arrows) with obliteration of chiasmatic cistern.

puted tomographic scan with contrast medium showed no change in the cerebellar mass. Vertebral angiography also suggested the presence of an avascular vermian lesion.

The patient was scheduled for a pneumoencephalogram and was again given corticosteroids; however, he had immediate remission of symptoms before the scheduled pneumoencephalogram and he therefore declined further studies. A repeat examination at this time revealed visual acuity of 6/4.5 (20/15) at distance and near in both eyes. Color vision in the right eye was 8½ plates correct out of ten, whereas color vision in the left was ten out of ten. The visual field in the right eye was intact except for several small, relative scotomas in the paracentral region. Results of ophthalmoscopic examination were normal. A computed tomographic scan showed no change from previous studies.

Corticosteroids were tapered slowly. Two weeks after corticosteroids were discontinued, however, visual acuity in the patient's right eye again deteriorated to 6/7.5 (20/25), and he could now identify only four out of ten color plates. The right visual field continued to show several small paracentral scotomas. A right afferent pupillary defect was now present. The left eye remained normal. Neurologic examination at this time revealed paravertebral spasm, lumbosacral tenderness, straight-leg raising ability to 30 degrees only, poor tandem gait, unstable Romberg test, decreased left knee reflex, and decreased sensation in the left lumbar 4 and 5 dermatomes. A noncontrast computed tomographic scan (Fig. 3) now showed a dense suprasellar mass that was not enhanced by use of contrast medium, and the lesion obliterated the chiasmatic cistern. Plain x-rays of the lumbosacral spine were normal. Views of the optic foramina (Fig. 4) showed symmetrical enlargement of the right optic foramen. Pneumonencephalography showed nonfilling of both the fourth ventricle and the chiasmatic cistern. Cerebrospinal fluid contained protein concentration of 252 mg/dl, glucose of 19 mg/dl, and no cells.

One week later, the patient underwent a right frontal craniotomy. A tumor was discovered that had displaced the intracranial portion of the right optic nerve upwards and invaded the right optic foramen. The right carotid artery was pushed laterally. The tumor obliterated the infrachiasmatic cistern and extended posteriorly to the hypothalamus. The optic nerve was decompressed. Frozen section suggested a malignant, small-cell tumor, Histologic examination of both the ventricular cerebrospinal fluid and of the permanent tumor sections confirmed a diagnosis of medulloblastoma.

Postoperatively, the patient's visual acuity improved to normal; however, he developed increasing sensory and motor loss in his lower extremities. Lumbar myelogram (Fig. 5) revealed a complete block at the L-3 level. Because of rapid worsening of his neurologic deficit, the patient underwent an L-2 to L-5 intradural laminectomy. An extensive, infiltrating tumor was present. The cell type of this tumor was typical medulloblastoma.

Fractioned radiotherapy to a total dose of 5,040 rads to the whole brain, 4,240 rads to the cervicothoracic spine, and 4,920 rads to the lumbosacral

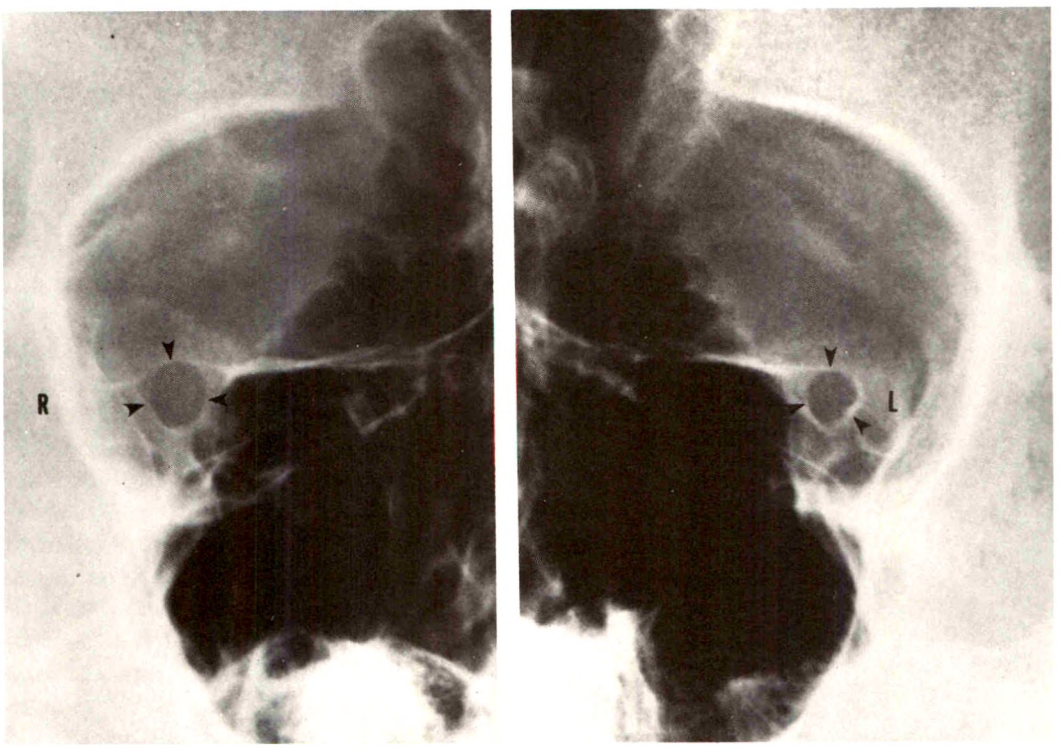

Fig. 4 (Hirst and associates). Optic foramina views (black arrows) showing symmetrical enlargement of right optic foramen.

spine was administered over the ensuing six weeks. Concurrent therapy with 2 mg of vincristine, intravenously weekly for six weeks, was also given. During the next four weeks, the patient's paraplegia partially resolved. Results of neuro-ophthalmologic examination remained normal. A computed tomographic scan before the patient's discharge from the hospital revealed no suprasellar or vermian masses (Fig. 6), although an enlarged fourth ventricle was noted. The patient remains well, with some residual paraplegia and no evidence of recurrence of intracranial tumor at 18 months after the craniotomy.

Discussion

Medulloblastoma is an uncommon tumor, which represents only 4%[1,2] of all tumors of the central nervous system; however, it represents about 20%[2] of all of the intracranial neoplasms in children under the age of 15 years. Although the prevalence is thus heavily skewed toward the younger population, it is noteworthy that various authors[3–9] have reported a rate of 18 to 53% in their personal series of medulloblastoma cases to have occurred in patients over the age of 16 years.

In most cases of medulloblastoma, the initial symptoms are caused by increased intracranial pressure or cerebellar infiltration, or both.[10] Spitz, Shenkin, and Grant[8] found that in adults with medulloblastoma, about 50% of patients had involvement of the cerebellar hemispheres, but the most common symptoms were of headache, nausea, and vomiting, with focal cerebellar symptoms appearing later.

Our case is unusual because the visual symptoms and signs suggested an optic neuritis, and the patient responded dramatically and repeatedly to corticosteroids. The rapid resolution of visual symptoms and signs with systemic corticosteroid therapy led to an initial diagnosis of probable demyelinating or inflammatory optic neuritis.

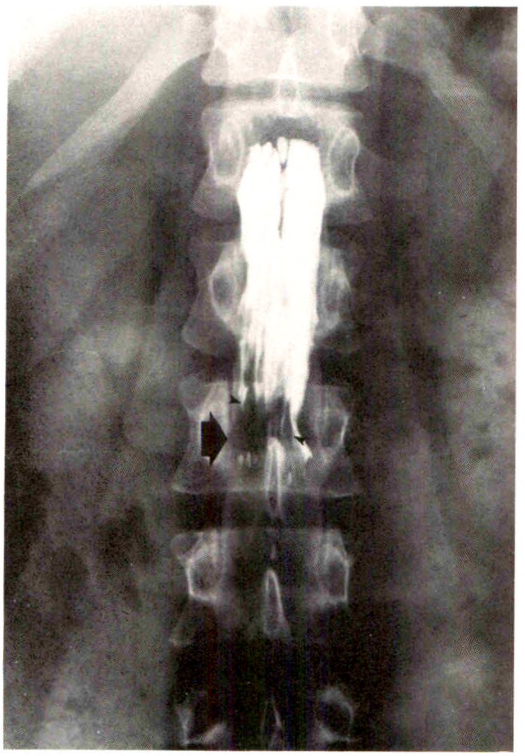

Fig. 5 (Hirst and associates). Lumbar myelogram revealing complete block at L-3 (large arrow), with small intradural nodular masses along nerve roots (small arrows).

It has been less well recognized that optic neuropathy from tumor compression may also respond to corticosteroids. Senelick and Van Dyk[11] reported a case in which the diagnosis of optic neuritis was supported by a favorable response to corticosteroid administration. The patient was later found to have a compression optic neuropathy caused by a pituitary adenoma. Additionally, two patients with solitary intracranial plasmacytomas have been described in whom an initial diagnosis of optic neuritis was made on the basis of sudden, unilateral visual loss associated with a central scotoma and an afferent pupillary defect, and was substantiated by dramatic improvement in vision after receiving systemic corticosteroids.[12,13] One of us (N.R.M.) has examined two patients with corticosteroid-sensitive optic neuropathies, both of whom were later found to have intracranial neoplasms. In one patient, the optic neuropathy was caused by a pituitary adenoma, and in the second patient, a craniopharyngioma accounted for bilateral visual loss that improved when corticosteroids were instituted.

There are two possible mechanisms by which corticosteroids may reverse dysfunction because of tumor compression. First, many tumors have an intrinsic inflammatory component. This component may respond to corticosteroids, thus resulting in a general reduction in the size of the tumor and a partial resolution of compressive symptoms and signs. Intracranial tumors may also produce a secondary inflammatory response at the interface of the tumor and normal cerebral tissue with the inflammatory component being partially responsible for visual symptoms and signs. In some cases, such as in the two intracranial plasmacytomas previously reported, the response to corticosteroids may have been caused by the direct reduction in size of the tumor itself. Conversely, improvement in visual function after corticosteroid administration to our patient with medulloblastoma may have been caused by resolution of inflammatory changes adjacent to the tumor. Whatever the mechanism, it is clear that the continued response of an optic neuropathy to corticosteroids does not guarantee a primary inflammatory cause.

Although visual disturbances have commonly been described in association with medulloblastoma, this has almost always been in the form of visual obscurations associated with papilledema.[10] Stroganova and Khokhlova[14] described 12 cases of optochiasmal arachnoiditis secondary to spread of medulloblastoma along the subarachnoid space, and Arnould and associates[15] described optic atrophy of unknown cause accompanying

Fig. 6 (Hirst and associates). Left, Postoperative contrast computed tomographic scan at level of posterior fossa showing enlarged fourth ventricle without compression. Right, Postoperative noncontrast computed tomographic scan of suprasellar region showing absence of suprasellar mass and normal chiasmatic cistern.

a posterior-fossa medulloblastoma. In our patient the operative finding of medulloblastoma, displacing the right optic nerve upward and extending into the right optic canal, explains the unusual visual manifestation. Although it is possible that the suprasellar medulloblastoma resulted from ventricular spread and invasion through the third ventricle, the most likely mode of metastasis was along the basal cisterns.

Although the prognosis of medulloblastoma occurring in adults is said to be better than that in children,[8] the management of this condition is mainly a combined radiotherapy and chemotherapeutic approach.[16] Our patient has shown a dramatic response to this combined therapy despite extensive intracranial and spinal axis involvement, which could not be surgically removed.

Our case emphasizes the necessity for clinical and radiologic reappraisal of any patient suspected of optic neuritis when the disease follows an atypical course. The apparent corticosteroid responsiveness of a suspected optic neuritis does not necessarily indicate an inflammatory cause, nor does it exclude a tumor process.

Summary

A 25-year-old man had signs of optic nerve dysfunction. A diagnosis of optic neuritis was made and was supported by rapid resolution of signs and symptoms with use of corticosteroids. After initial negative radiologic investigations, his corticosteroid dosage was tapered, and the recurrence of his symptoms and signs prompted repeat computed tomographic scans. A suprasellar mass and a posterior-fossa mass were observed, and frontal craniotomy disclosed typical me-

dulloblastoma, confirmed histologically. Although visual signs and symptoms in medulloblastoma have been reported secondary to optochiasmatic arachnoiditis and to papilledema, to the best of our knowledge this is the first reported case in which direct compression of the optic nerve has occurred as a result of extension of a posterior-fossa medulloblastoma. The favorable response of this compressive tumor to corticosteroids, stimulating an inflammatory optic neuritis, emphasizes the importance of reassessing any optic neuritis that follows an atypical course.

ACKNOWLEDGMENT

Frederick Isaacson, M.D., Taylor Medical Group, Towson, Maryland, provided Figure 1.

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MYASTHENIC SUSTAINED GAZE FATIGUE

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Demonstrable muscular fatigue is the essential sign of myasthenia gravis. Although progressive weakening of skeletal muscles with repetitive contraction does occur, its assessment is difficult because of marked variability of normal limb strength. Therefore, the clinician has traditionally focused attention on the levator palpebrae superioris muscles that frequently show reliable fatigue phenomenon. We examined two patients who showed fatigue of extraocular muscles evoked by sustained conjugate lateral gaze.

Case 1—A 46-year-old man had a five-day history of horizontal double vision, worse in the left eye. A similar episode five months earlier had spontaneously resolved over a two-week interval. His medical history was unremarkable and the patient denied symptoms of systemic muscular weakness.

Results of the general physical examination, including a thorough neurologic examination, were unremarkable. Results of neuro-ophthalmologic examination showed 2 mm of left blepharoptosis unassociated with either an eyelid twitch sign[1] or fatigue phenomenon. Orbicularis oculi muscle strength was normal without fatigue.[2] Ocular movements were initially unimpaired. However, if left gaze was sustained the right eye slowly drifted toward the primary position (Fig. 1). The eyelid position was variable as medial rectus fatigue developed. After one minute of respite, the same sequence of events was shown. The visual acuity, visual fields, pupils, anterior segments, and fundi were normal.

Intravenous injection of 10 mg of edrophonium chloride was initially interpreted as equivocal but repeat testing resulted in a reduction of blepharoptosis and prolonged adduction of the right eye during sustained lateral gaze. After negative results from thyroid function studies and normal results from anterior mediastinum polytomography were found, the patient received an alternate-day course of corticosteroids combined with pyridostigmine bromide. Normal eyelid position and full ocular rotations without evidence of sustained gaze fatigue constituted an excellent therapeutic response.

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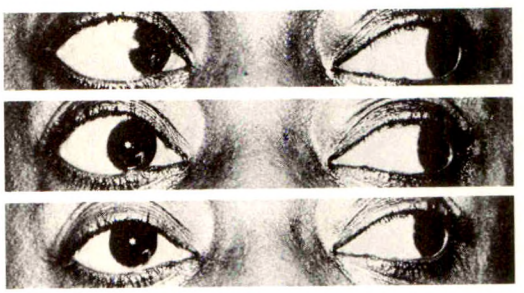

Fig. 1 (Osher and Glaser). Top, Initial eye movements in left gaze appear full. Middle, Sustained lateral gaze shows adduction fatigue. Bottom, Right eye drifts back toward primary position.

Case 2—A 53-year-old man had an abrupt onset of horizontal double vision. He was otherwise asymptomatic and in good health. Bilateral eyelid retraction and periocular eyelid swelling were present. After closing both eyes, the patient could briefly maintain single vision, but a variable exophoria would consistently become a large alternating exotropia. On initial attempt at left gaze, adduction of the right eye showed minimal limitation (Fig. 2). On sustained left gaze, however, the right eye displayed a molasses-like gradual drift toward primary position. The left medial rectus muscle showed a similar fatigue pattern during sustained right gaze (Fig. 3). Dissociated nystagmus in the abducting eye was notably absent. Vertical gaze was preserved although a prominent eyelid lag was observed on

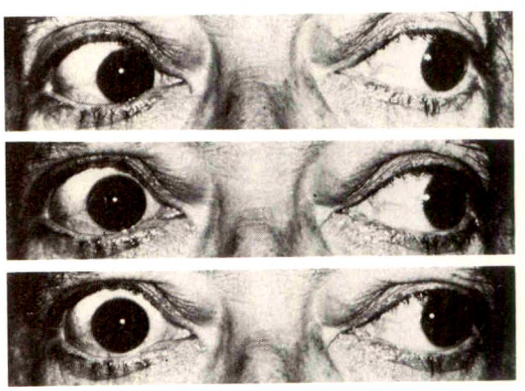

Fig. 2 (Osher and Glaser). Top, Initial eye movements in left gaze show minimal adduction limitation. Middle, As right medial rectus fatigue develops the right eye drifts back toward primary position despite efforts to sustain left gaze (bottom).

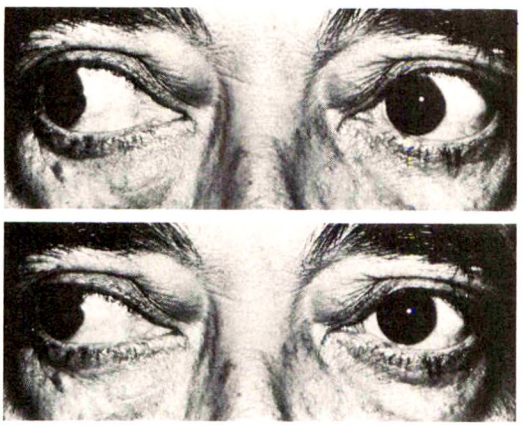

Fig. 3 (Osher and Glaser). Sustained right gaze (top) shows progressive fatigue of left medial rectus (bottom).

Fig. 4 (Osher and Glaser). Sustained left gaze (left) shows left lateral rectus fatigue as a cholinergic complication of therapy (right).

downgaze. Intravenous injection of 5 mg of edrophonium chloride eliminated the exotropia in primary position and lateral gaze could be sustained without adduction fatigue.

Neurologic examination and anterior mediastinum tomography were unremarkable. Because of eyelid retraction and lag, an endocrine evaluation was undertaken and the diagnosis of hyperthyroidism was established by the following positive results of thyroid studies: serum T_4 isotope, 13.9 μg/100 ml; serum T_3 concentration, 240 ng/100 ml; 24 hour radioactive iodine uptake, 54%; baseline serum thyrotropin, 2.8 μ/ml and 2.6 μ/ml 30 minutes after injection of protirelin.

Methimazole, pyridostigmine bromide, and alternate-day administration of prednisone were initiated. After a difficult course characterized by the development of esotropia and bilateral abduction paresis with sustained gaze fatigue (Fig. 4) as a cholinergic complication, all medications were tapered and discontinued. Subsequently, a complete remission was achieved and the patient remains asymptomatic one year after the onset of his illness.

Discussion

Pathologic muscular fatigue is the primary sign of myasthenia gravis. Marked variability of limb strength makes such assessment difficult, so the clinician has traditionally evaluated the levator palpebrae superioris muscle for evidence of fatigue. During sustained upgaze, increasing blepharoptosis may become apparent.[3] Cogan's[1] eyelid twitch sign is a transient eyelid retraction (overshoot). This results in the initial blepharoptosis, evoked by rapid refixation from downgaze to primary position. Diurnal variation of eyelid position characterized by increasing blepharoptosis as the day progresses also reflects prolonged levator muscle fatigue.

The recently described "peek" sign of myasthenia represents a specific manifestation of orbicularis fatigue.[2] Upon gentle eyelid closure, the orbicularis muscle contracts, initially achieving eyelid apposition. With sustained eyelid closure, however, the orbicularis muscle rapidly fatigues and the palpebral fissure widens, thereby exposing sclera. The patient thus appears to "peek" at the examiner. Afternoon ectropion is the parallel to diurnal variation of eyelid position and probably reflects gradual orbicularis fatigue as the day progresses.[4]

Eye movement fatigue has recently been shown by electro-oculography,[5] whereby the amplitude and maximum velocity of repetitive saccades progressively decreased over three-minute intervals. However, extraocular muscle fatigue may be detected by clinical observation alone as described here. In order to elicit this sign, careful observation of globe position during sustained extreme lateral gaze is required. While the patient attempts to maintain either lateral or vertical gaze, a characteristic slow drift toward the primary position occurs. A cursory glance at ocular motions will certainly miss this phenomenon, because ocular muscle fatigue has a momentary or delayed onset. Intravenously injected edro-

phonium will eliminate the sustained gaze fatigue sign, thereby confirming the diagnosis of myasthenia gravis.

Summary

Sustained gaze fatigue was found in two patients whose diplopia was the first manifestation of myasthenia gravis. Although ocular excursions initially appeared full, a slow drift toward the primary position occurred during sustained extreme gaze. This motility pattern signifies pathologic extraocular muscle fatigue and strongly implicates myoneural junction disease. When myasthenia gravis is suspected, the presence of sustained gaze fatigue provides a tentative clinical diagnosis to be confirmed by pharmacologic testing.

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OPHTHALMIC MINIATURE

GLAUCOMA

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ISOLATED OCULOMOTOR PALSY AFTER MEASLES IMMUNIZATION

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Isolated oculomotor nerve palsy occurs infrequently in children.[1] Most cases are congenital, or are secondary to blunt trauma and infectious processes.[2] Other rare causes include neoplasms, aneurysms, and ophthalmoplegic migraine. The case reported here may be related to immunization. To the best of our knowledge, this is the first detailed case report of isolated oculomotor nerve palsy after measles immunization.

CASE REPORT

A 17-month-old boy who was alert and active was admitted elsewhere because of the rapid onset of a right third cranial nerve palsy. The patient had been in excellent health until ten days before admission, when he developed a minimal upper respiratory tract infection with a cough and mild fever. His mother had similar symptoms. Two weeks before admission, the patient had a measles immunization. The vaccine was an attenuated virus preparation achieved by multiple passage of Edmonston virus. Two days before admission, he became irritable and had an episode of vomiting. The day before admission, his mother noted that the boy's right eye was partially closed, and, on the day of admission, that the eye was totally closed. Medical history and family history were unremarkable. There was no history of migraine in the immediate family.

Results of an examination at the time of admission were normal, except for a complete right third nerve palsy (Fig. 1). Results of the ophthalmoscopic examination were normal and vision was thought to be normal. Results of the following laboratory tests were normal: complete blood cell count, sedimentation rate, electrolytes, and glucose. Cerebrospinal fluid, protein, and glucose were normal. Viral and bacterial cultures of cerebrospinal fluid and bloods were negative. Skull x-rays, electroencephalogram, and computed axial tomograms of the brain with and without contrast were normal. A purified protein derivative skin test was negative. An intravenous pyelogram, to rule out a retroperitoneal mass, was within normal limits. Bone marrow, to exclude a malignant or infectious infiltrate, showed a nonspecific lymphocytosis, which was normal for his age. Examination of acute and convalescent sera for encephalitic and respiratory viral syndromes showed changes only in the measles titer (1:64 acute to 1:32 convalescent), compatible with postimmunization titers.

While in the hospital, the patient's blepharoptosis improved. On the fifth day of hospitalization, notable improvement in his oculomotor nerve function was evident; his right pupil responded to light, and he could elevate his right upper eyelid (Fig. 2).

One month later, his right upper eyelid and pupil had recovered completely, although there was weakness in adduction of the right eye. Two months later, his right oculomotor palsy resolved completely. The patient did not have any recurrences or other illness during the next 14 months.

DISCUSSION

In 1903, Smiley[3] reported a case of oculomotor paralysis after vaccination, which gradually diasppeared. Rosen[4] was impressed by the frequency of ocular complications after vaccinations. Without

Fig. 1 (Chan, Sogg, and Steinman). At the time of admission, the patient showed a complete right third nerve palsy.

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Fig. 2 (Chan, Sogg, and Steinman). At the time of discharge (on the fifth day of hospitalization), there was partial recovery of the third nerve palsy.

giving specific details, he mentioned several cases of isolated ocular muscle palsies after immunization, all of which had completely recovered after three or four weeks. Our patient's course may be explained by the use of attentuated measles virus for immunization, although oculomotor paresis from immunization is rare (F. B. Walsh, personal communication, 1978). The serum antibody titers indicate effective immunization against measles.

The differential diagnosis includes brain tumor, cerebral aneurysm, arteriovenous malformation, or trauma. These all seem unlikely given the normal computed tomography scan, skull x-ray, electroencephalogram, spinal fluid analysis, and subsequent clinical course. We cannot totally exclude a vascular disorder of the brain without arteriography. Given the patient's clinical course, we believed this was unwarranted. Ophthalmoplegic migraine causes recurrent oculomotor paralysis.[5] The initial signs are severe and include a throbbing headache, followed by ophthalmoplegia that may last hours or days.[6] Between attacks, the ocular motility is normal. It usually recurs within weeks or months.[7] After 14 months of follow-up, there was no recurrent oculomotor palsy in our patient. The rapid recovery of the palsy without aberrant regeneration of the third nerve makes neoplastic invasion, aneurysm, or trauma unlikely.[8]

Isolated oculomotor nerve palsy may be part of viral encephalitis. It has been recorded as the initial neurologic sign in meningitis[9,10] and other systemic infections with various viral causes, including infectious mononucleosis,[11] chicken pox,[12] mumps,[13] and Coxsackie virus A_9 infection.[14] Knox, Clark, and Schuster[15] described lateral rectus palsy in children, occurring after an apparently benign illness. The palsy developed in association with otitis media and its complications, or with neuritis after systemic viral illness. Our patient had right oculomotor nerve palsy after a mild upper respiratory tract syndrome. However, the finding of a changing measles antibody titer in the presence of negative serum and blood titers of other viral diseases, as well as normal complete blood cell count, and cerebrospinal fluid findings implicates the measles immunization as an important factor in the cause of the third nerve palsy in the present case.

Summary

A 17-month-old healthy boy had a rapid onset of right oculomotor nerve palsy, and spontaneous recovery after measles immunization. Results of computed tomography scan, skull x-ray, chest x-ray, intravenous pyelogram, and bone marrow examination were all normal. Serum antibody titers showed effective measles immunization.

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Ophthalmic miniature

I think it was his eye! Yes, it was this! One of his eyes resembled that of a vulture—a pale blue eye with a film over it. Whenever it fell upon me, my blood ran cold, and so, by degrees, very gradually, I made up my mind to take the life of the old man and thus rid myself of the eye forever.

Edgar Allan Poe
The Telltale Heart

OCULAR *AEROMONAS HYDROPHILA*

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Vancouver, British Columbia, Canada

Aeromonas hydrophila is a gram-negative rod whose natural habitat is man's aquatic environment.[1] It rarely causes infection in humans. Its infrequent implication in human disease may be attributable in part to its misidentification.[2] As described, such infections have been enteric, local, or septicemic.[3] Patients with chronic liver disease, malignant disease, and suppression of immunity are particularly[4–6] prone to invasive disease, and local infection is usually the result of injury and contamination by soil or water.[7,8]

Infections of the eye have been described on two previous occasions.[9,10] We describe four patients from whose eyes the organism was isolated in this hospital laboratory since 1970.

METHODS

Bacterial identification was by standard methods. *Aeromonas hydrophila* is strongly hemolytic, oxidase-positive, motile, hydrogen sulfide negative, and indole-positive. It ferments glucose, sucrose, maltose, and mannitol. It ferments lactose weakly. Antimicrobial susceptibility testing was by agar disk diffusion.

CASE REPORTS

Case 1—An 87-year-old woman was admitted in 1972 for elective cataract extraction. She had a left ectropion dating from surgical excision of a squamous cell carcinoma of the left lower eyelid 14 years earlier. At the time of her admission, she had an acute left-sided conjunctivitis that had been present for four days. She was afebrile and her white blood cell count was 4,400/mm³. Her left eye showed a pure culture of *A. hydrophila.* She was treated with chloramphenicol 0.5% eyedrops given every two hours while awake and she recovered without incident. At the time of cataract extraction, which was deferred until six months later, there were no infectious complications and the preoperative eye swab showed no growth.

Case 2—A 52-year-old man was seen in 1971 because of chest pain. At that time, the patient was noted to have severe, long-standing bilateral conjunctivitis. He wore hard contact lenses. He was afebrile and his white blood cell count was normal. Bacteriologic sampling of the conjunctiva showed *A. hydrophila.* There was no record of treatment or follow-up.

Case 3—A 75-year-old man was operated on in 1971 for a cataract in the left eye. At the time of surgery, a swab was obtained for culture and this showed a pure growth of *A. hydrophila.* Chloramphenicol ophthalmic solution 0.5% was applied at the time of surgery and every four hours thereafter. He also was given 250 mg of tetracycline orally four times daily for two days. His maximum temperature was 37.4°C and white blood cell count was 4,000/mm³. He was discharged from the hospital nine days later with no evidence of infection at any time. Six months later, he was admitted for needle excision of a cyclitic membrane complicating the cataract surgery. His conjunctival swab showed no bacteria and there was no evidence of infection.

Case 4—A 7-year-old boy was admitted in 1977 because a safety pin had penetrated his right eye on the day before admission. A subconjunctival hemorrhage was noted, but there was no corneal laceration. A cellular response was evident in the anterior chamber and ultrasound examination of the orbit showed debris in the anterior part of the vitreous cavity. The lens was cataractous with an organized white fibrous membrane behind it. Anterior vitrectomy and lensectomy were performed on the eye with no complications. At surgery, 5 ml of gentamicin ophthalmic solution (0.5%) was used to irrigate the eye and the patient was given 20 mg of gentamicin intramuscularly every eight hours for seven days, and 250 mg of cloxacillin was given intravenously every six hours for ten days. Gentamicin eyedrops and chloramphenicol eyedrops were instilled in the conjunctival sac every two hours while awake. His white blood cell count was 7,700/mm³ and his maximum temperature during his two-week hospital stay was 37.8°C on one occasion. A conjunctival swab taken at surgery showed *A. hydrophila* and *Hemophilus influenzae.* There was no clinical evidence of infection of the eye at any time during his hospital stay or after discharge.

All the isolates of *Aeromonas* from these four

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cases were sensitive to tetracycline, chloramphenicol, and gentamicin. The *H. influenzae* isolated from Case 4 was not tested for antimicrobial susceptibility but all isolates at the time were considered sensitive to chloramphenicol.

Discussion

These four cases show the two possible roles of *A. hydrophila* in the eye. It may cause infection as exemplified by Cases 1 and 2, and it can cause asymptomatic colonization as shown by Cases 3 and 4.

There are two previous reports of *Aeromonas* infections in the eye[9,10] in which all three patients had suffered injury; one was struck by a seashell, one had a foreign body injury on an offshore oil rig, and one received an injury during a dynamite blast. Neither of the two patients with clinical infection described here gave a history of such injury.

The patient described in Case 1 had a stenosed lacrimal duct and ectropion with chronic tearing, a condition conducive to the development of chronic conjunctivitis.[11] This patient seemed to have an acute four-day illness rather than a chronic infection. However, it is possible that the stenosed tear duct and ectropion were etiologic factors.

There was no mention in the hospital record of Case 2 of the means of storage of the patient's contact lenses. Solutions used for this purpose may get contaminated with other water bacteria, and irritation of the cornea and conjunctiva by contact lenses together with contamination of storage solution may have been the cause of this patient's chronic conjunctivitis.

It is not clear whether the presence of *Aeromonas* in the conjunctiva in Case 3 was caused by transient contamination or by chronic colonization. Certainly, *Aeromonas* is not frequently encountered in the eye swabs cultured in our laboratory, and this is in accord with the report by Feaster, Nisbet, and Barber.[10]

Case 4 is more typical of the type of patients previously reported to have *Aeromonas* ophthalmic infection in that the patient suffered a penetrating injury.[9,10] However, he did not develop clinical signs of infection. This may have been the result of vigorous antimicrobial therapy and effective surgery.

According to Feaster, Nisbet, and Barber,[10] the clinical features of *Aeromonas* infections in the eye are nonspecific. However, they state that the association of acute infection of the eye with a history of contamination by water or soil may be significant. The cases reported here indicate that lacrimal duct stenosis and the wearing of contact lenses may also be significant.

The antimicrobial susceptibility patterns of the four isolates reported here, as well as the reports of others, indicate that chloramphenicol or aminoglycoside antimicrobials are the agents of choice in treatment. All strains are resistant to ampicillin. Cephalosporins, carbenicillin, and ticarcillin disodium are not as effective.[4,9,12,13]

With increased awareness of this organism as a potential pathogen, and with appropriate bacteriologic identification procedures, including the routine use of the oxidase test in the identification of gram-negative rods, *Aeromonas* may be recognized more often in the future as an ophthalmic pathogen.

Summary

Aeromonas hydrophila was isolated from the eye swabs of four patients. Two were thought to have definite clinical infection; one had chronic conjunctivitis complicating the wearing of contact lenses, and the other had acute conjunctivitis associated with ectropion and lacrimal duct stenosis. Two patients had no clinical evidence of infection. Both of them had swabs taken at the time of surgery. One had a cataract extraction and the other had a lensectomy and vitrectomy for a penetrating injury. The outcome was satisfactory in the two patients in whom colonization occurred, and in the patient

with acute conjunctivitis, all of whom received chloramphenicol with or without gentamicin. The fourth patient was not followed up.

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THE OCULAR MICROBIOLOGY AND IMMUNOLOGY GROUP 1979 MEETING

The 1979 meeting of the Ocular Microbiology and Immunology Group was held in San Francisco, California, Nov. 3. Robert Burns moderated the morning session and G. Richard O'Conner the afternoon session.

After a few moments' silence in memory of our colleague, Samuel J. Kimura, who died in Granada, Spain, on Oct. 15, after an automobile accident, the morning session began with a presentation by W. J. O'Brien, J. L. Taylor, J. Pach, J. DeCarlo, D. W. Clough, and R. O. Schultz. Their paper dealt with the efficacy of arabinosylthymine (ARA-T). Arabinosylthymine 1% was given topically to rabbits five times a day for five days to test its effect on herpetic keratitis. The authors concluded that ARA-T was an effective and catabolically stable antiviral agent whose toxicity for Chang conjunctival cells was relatively low. The group did not test the systemic use of the drug or its immunosuppressive activity.

H. E. Kaufman performed a similar study and found arabinosylthymine to be much less effective topically than adenine arabinoside or acycloguanosine.

R. H. Poirer discussed the aqueous penetration of trifluoridine, adenine arabinoside 5-monophosphate, and acycloguanosine. In the aqueous humor there was no detectable trifluoridine, the levels of adenine hypoxanthine (the metabolite of adenine arabinoside 5-monophosphate) were meager, and the levels of acycloguanosine were significant. The penetration was improved if the corneal epithelium was removed. During the discussion it was mentioned that since trifluoridine was not stable at the pH of aqueous, determining its levels in the aqueous could be misleading. The discussor believed cellular concentration levels were important but not aqueous levels.

E. D. Varnell and H. E. Kaufman produced a stromal herpetic lesion in rabbits by inoculating them midstromally with the RE strain of herpesvirus. The effect of acycloguanosine was investigated. Although 60 mg of acycloguanosine/kg of body weight given intravenously once a day caused only minimal improvement, subcutaneous injections of 30 mg/kg of body weight twice a day caused significant improvement, and acycloguanosine and adenine arabinoside 5-monophosphate in combination had the most therapeutic effect.

A. H. Wander and H. E. Kaufman tried to establish a varicella zoster animal model. Delta herpesvirus caused a varicella-like disease in monkeys, and delta herpesvirus infections protected animals against varicella infection. Iritis could be produced in some immune animals by injecting delta herpesvirus into the anterior chamber. The authors hypothesized that delta herpesvirus infections in patas monkeys may be a successful model for varicella zoster infections in man.

M. P. Langford, M. Yin-Murphy, J. C. Barber, S. Baron, and G. J. Stanton reported finding neutralizing activity against Coxsackie virus type A24 in the tears of patients with Coxsackie virus conjunctivitis during an outbreak in Singapore in 1975. Specifically, the antiCoxsackie virus type 24 neutralizing activity was detected in 67% of the tear samples collected one to four days after the onset of the conjunctivitis, in 56% of the tear samples collected 15 to 110 days after the onset, and in none of the tears of normal individuals. Interferon activity was detected in 38% of the tear samples collected from patients with acute disease. The

fibroblast interferon was probably produced by conjunctival epithelial cells, its early appearance suggesting that it might play some defensive role in Coxsackie virus infection.

A. R. Taylor, A. M. Silverstein, R. A. Prendergast, C. R. Dawson, and J. Schachter believed they had developed a model of cicatrizing trachoma in cynomolgus monkeys by reinfecting them repeatedly with Bour strain *Chlamydia trachomatis*. A chronic follicular conjunctivitis, follicles on the upper tarsal conjunctiva, and finally trachomatous tarsal conjunctival scarring were all produced. The presence of chlamydiae had been verified by Giemsa staining and the fluorescent-antibody technique. Dr. Thygeson questioned the validity of the model because the Bour strain is type F, and because repeated inoculations were required to produce scars and corneal vascularization.

D. B. Mark and J. P. McCulley presented two cases of Reiter's keratitis. The corneal changes included subepithelial and anterior-stromal infiltrates, ragged epithelial erosions, and a disciform stromal lesion. The authors reported finding an inclusion body in an epithelial cell. In the discussion it was pointed out that errors in interpreting scrapings are common.

C. R. Dawson, B. Togni, L. Lauricella, and B. Nichols studied the distribution of mucosubstances on the conjunctivas and corneas of guinea pigs by staining specimens with ruthenium red, alcian blue, and tannic acid, and then examining them by transmission electron microscopy. A cell coat (glycocalyx) was seen tightly apposed to the surfaces of all conjunctival and corneal cells. Goblet cells were numerous in the conjunctiva, particularly over the upper tarsus, and they secreted mucous granules from their free surfaces. The mucous coat was loosely attached to the tips of the microvilli; in contrast, the glycocalyx was part of the cell membrane.

T. E. Gillette identified lysozyme in from 20 to 50% of acinar and ductular epithelial cells of both main and accessory lacrimal glands. The fluorescent staining was confined to the apices of the cells.

T. O. Bennett, R. Epstein, and J. Sugar used the mixed lymphocyte culture and serotyping to delineate the major canine histocompatibility complex. Although seven of eight animals matched at the D locus maintained clear grafts in vascularized beds, all of nine unmatched animals rejected their donor corneas.

J. C. Fleming, F. R. Reid, and T. O. Wood evaluated the ability of fluorometholone, prednisolone acetate, and decadron phosphate to suppress corneal allograft reactions in rabbits. In their model the drugs were equally effective.

D. J. Coster, W. F. I. Shepherd, T. Chin-Fook, B. H. Jones, and N. S. C. Rice used cyclosporin A to suppress corneal graft reactions in rabbits. Short-term topical treatment with the drug prolonged graft survival.

G. Smolin, M. Okumoto, M. Friedländer, and R. Cyr used oxazolone (a skin sensitizer) to treat rabbit eyelid papillomas induced by the Shope papilloma virus. In sensitized animals the application of oxazolone to the tumor resulted in its regression. The mechanism of action of this drug has yet to be determined.

M. R. Allansmith, K. J. Bloch, R. S. Baird, and K. J. Sinclair measured the change in vascular permeability that accompanies anaphylaxis. Systemic anaphylaxis induced by egg albumin or worm antigen increased the vascular permeability of the small intestine, but only the egg albumin induced a similar change in the ocular tissues.

M. B. Abelson and G. K. Yamamoto determined the effect of antazoline and the vasoconstrictor, naphazone, individ-

ually and in combination, on the signs and symptoms induced by the topical instillation of histamine (50 μg/ml). Antazoline reduced the itching and naphazoline the redness. In combination the drugs were more effective on both symptoms than either drug alone. The observers noted no alteration in corneal sensitivity.

S. A. Fowler and M. R. Allansmith studied the surfaces of continuously worn contact lenses by scanning electron microscopy. All of the continuously worn lenses were completely covered with a matted coating that was for the most part smooth and had no bare spots. The coating was composed of trabecular and granular mucus-like material and some bacterial forms.

J. H. Lass, J. Haaf, C. S. Foster, and C. Belcher presented eight cases of *Serratia marcescens* keratitis. Most of the patients were immunosuppressed or compromised (elderly, taking corticosteroids or antibiotics, wearing contact lenses, and the like). Treatment with gentamicin, bacitracin, cephazolin, or carbenicillin was effective. Most patients had visual acuities of 6/12 (20/40) or better after completion of treatment.

T. M. Raber, P. R. Laibson, G. H. Kurz, and V. B. Bernardino presented four cases of *Pseudomonas* corneal-scleral ulcers. Most of the patients had some debilitating disease (for example, herpes zoster) or were being treated with corticosteroids. Despite intensive antibiotic treatment, all eventually required enucleation or evisceration. In the discussion it was mentioned that cryotherapy in conjunction with antibiotics might be therapeutic.

P. Asbell and S. Stenson discussed their 30-year laboratory experience with bacterial corneal ulcers. The recovered organisms were *Staphylococcus* (48%), *Moraxella* (16%), *Pseudomonas* (8%), and the pneumococcus (6%). If the culture was positive, 65% of the scrapings were positive, but if the culture was negative, only 29% of the scrapings were positive. There were no definite trends in the frequency of recovery except for a reduction in the number of recoveries of *Moraxella*, possibly owing to a reduction in the number of alcoholic patients referred to the clinic. Whatever the organisms, gentamicin and bacitracin were the most effective antibiotics.

M. Okumoto, G. Smolin, and L. Leong-Sit examined the effect of corticosteroids on a gentamicin-resistant *Pseudomonas* keratitis that was treated concomitantly with a corticosteroid and gentamicin (first three days), and then with tobramycin alone. More organisms were present on day 3 in corneas receiving corticosteroids and antibiotics than in corneas treated with antibiotics only. After three weeks the clinical picture was the same in both groups. It was pointed out that *Pseudomonas* infections often recur in clinically quiet eyes.

J. D. Hofbauer and T. H. Pettit studied the microbial flora of donor tissue stored in M-K medium. Cultures were positive in 35% of the cases, but the majority had only a few colonies. The most common isolate was *Staphylococcus epidermidis* (44%). During the discussion, several participants stated their opinion that many false-positive results may have been produced by the authors' technique. A 4 to 5% positive culture rate was thought to be a much more likely figure.

P. C. Ho and D. M. O'Day reported four cases of posttraumatic *Bacillus cereus* endophthalmitis. In each case, a fulminating endophthalmitis developed, accompanied by fever and leukocytosis. Despite prompt treatment, all eyes were lost.

G. A. Peyman, M. Rhaishard, and T. O. Bennett reported on 20 patients with culture-proven endophthalmitis on

whom vitrectomies were performed after diagnosis. Ten of the 20 retained visions of 6/30 (20/100) or better. During the discussion it was mentioned that when gram-negative organisms caused the endophthalmitis, nothing seemed to salvage the eye; that when gram-positive organisms were the cause, subconjunctival and intravitreal antibiotics might be as effective as vitrectomy and antibiotics; and that if the recovered organism was *Staphylococcus epidermidis* and the treatment appropriate, good visual results could be anticipated.

R. A. Eiferman discussed the intraocular penetration of amikacin sulfate. Bactericidal levels were not reached consistently no matter what the route of administration. Melanin-binding of the aminoglycosides was discussed.

M. Barza, A. Kane, and J. Baum discussed the clearance of intravitreal carbenicillin in the eyes of rabbits. Systemic probenecid doubled the half-life of intravitreal corbenticillin in the ocular tissues and fluids.

J. H. Brinser discussed the use of Snyder's medium as an alternative to media containing chloramphenicol-cycloheximide for the isolation of fungi and yeasts from ocular sources. Snyder's medium was found to be useful for isolating saprophytic fungi.

R. L. Abbott, R. G. Webster, and W. H. Spencer presented a case of posttraumatic phycomycosis (caused by *Rhizopus*) that affected the anterior segment of the eye. After intensive but unsuccessful antifungal medical therapy, a planned extracapsular keratoplasty was performed. The patient received postoperative antifungal therapy for four months. Keratoplasty repeated 27 months later showed Phycomycetes-like organisms in the cornea and chamber membrane.

At the business meeting that followed the morning session, the attending members decided to hold the 1982 meeting immediately preceding the International Congress of Ophthalmology in San Francisco. Some logistic problems were anticipated. The 1980 and 1981 meetings will be in Chicago and Atlanta, respectively.

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PAN-AMERICAN ASSOCIATION OF OPHTHALMOLOGY—40 YEARS

In 1938 Harry S. Gradle of Chicago, then president of the American Academy of Ophthalmology and Otolaryngology, conceived the Pan-American Association of Ophthalmology to bring together ophthalmologists in North and South America to promote the exchange of scientific knowledge, increase professionalism, and encourage friendship and understanding among eye specialists in the western hemisphere. An organizational meeting in 1940 brought together Moacyr Alvaro of San Paulo, Brazil, and Conrad Benrens of New York City. The first Pan-American Congress of Ophthalmology was held in Cleveland in 1940 in conjunction with the American Academy of Ophthalmology and Otolaryngology meeting.

From the beginning the Pan-American Association of Ophthalmology was dedicated to education. When Benjamin F. Boyd of Panama succeeded Moacyr Alvaro as executive director, educational activities rapidly increased. The Pan-American Congress, which originally met every four years, is now held every two years. Two Congresses meet in Latin American countries to every one held in North America. They have become increasingly important and over 1,000 ophthalmologists attended the 1979 Congress in Miami, Florida (Am. J. Ophthalmol. 87:722, 1979).

The Association sponsors two basic clinical science courses for Latin American residents. The oldest of these, at the University of Puerto Rico, is an intensive four-month course with classes six days weekly. Instruction is provided by the faculty of the Puerto Rico University and by outstanding teachers from the United States, Canada, and Latin America who donate their services. The students are 27 ophthalmology residents who are selected through national contests supervised jointly by the Pan-American Association of Ophthalmology and the national society in each of 18 Latin American countries. Three hundred forty residents have completed this course; some 140 of these are currently teaching in medical schools.

An Andean program was established in 1971 with particular emphasis on the skills required by ophthalmologists who

practice in the remote regions of Colombia, Ecuador, Venezuela, Peru, and Chile.

The Visiting Professor project is one of the most progressive and effective teaching programs in ophthalmology. The Pan-American Association arranges an itinerary and plans meetings for two or more specialists to visit different countries and to share their expertise with local ophthalmologists. Since the program began in 1962, more than 225 visiting professors have participated and more than 10,000 ophthalmologists have attended the sessions.

In recent years the Pan-American Pathology Club, the Pan-American Microsurgical Association, the Pan-American Glaucoma Club, and the Pan-American Strabismological Society have been established under the aegis of the Pan-American Association. These groups meet at the time of the Congress and bring together individuals of similar interests from North and South America.

Inasmuch as Latin America has few major eye centers there are ambitious plans for future activities. Ophthalmic basic science manuals in Spanish are necessary. A method must be provided to teach outstanding Latin American ophthalmologists new techniques in the United States. Monolingual ophthalmologists of major cities in the United States must learn to manage patients speaking their native Spanish. Ophthalmic teaching centers must be developed in Latin America. To maintain forward progress meetings must be held more frequently than every two years.

The Association currently has 3,500 members. Membership is open to all ophthalmologists in the Western Hemisphere. Membership dues are $100 annually. For information on joining or renewing membership, write H. Dunbar Hoskins, Jr., M.D., Secretary-Treasurer for the Northern Hemisphere, #1 Tara View Road, Tiburon, CA 94920; or Dr. Francisco Conteras, Secretary-Treasurer for the Southern Hemisphere, Ramon Ribeyro 525, Miraflores, Lima, Peru. The next Congress is scheduled for Acapulco, Mexico, May 10-15, 1981.

FRANKW. NEWELL

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Isosorbide and Isorbide Dinitrate

Editor:

Isosorbide (Ismotic) is a new hyperosmotic agent that has recently been introduced in the United States for the short-term reduction of intraocular pressure. Another compound, isosorbide dinitrate (Isordil) has been used in this country by internists for many years for the treatment of angina pectoris. The similarity between the generic names of the two compounds is potentially confusing. The hyperosmotic, isosorbide, is supplied only as a liquid, whereas isosorbide dinitrate is a tablet, which possibly will lessen this confusion. Nevertheless, with the increasing trend toward the use of generic names, the internist and ophthalmologist should be aware of the potential problems, which might be lessened by the use of the full generic or brand name.

EDWARD G. BUCKLEY, M.D.
AND
M. BRUCE SHIELDS, M.D.
Durham, North Carolina

The Incidence of Fundus Lesions in Septicemia

Editor:

I read with interest the recent article, "The incidence of fundus lesions in septicemia," by S. Meyers (Am. J. Ophthalmol.

88:661, 1979), but disagree that this study demonstrates that septicemia is related to the pathogenesis of fundus lesions. There were major shortcomings in the methodology of this study. Of the 23 patients with ocular findings, seven had "sepsis" with only *Staphylococcus epidermidis*. This bacterium is almost always a blood culture contaminant[1,2] and causes true bacteremia in rare instances of urinary tract infection or infected prosthesis.[2,3] No mention was made of these underlying conditions in the listed medical diagnoses. Secondly, no ocular examination was performed on a control patient population, matched by age, sex, race, underlying medical conditions, and the like, but without bacteremia; in order to demonstrate a genuinely increased incidence of fundus lesions related to bacteremia (especially in the absence of bacterial endocarditis). Ophthalmologic examination ideally should be done without prior knowledge of which patients have bacteremia.

I believe more comprehensive prospective studies are needed before it can be accepted that septicemia, other than secondary to bacterial endocarditis, should be considered in the differential diagnosis of cotton-wool lesions, hemorrhages, or white centered hemorrhages in the retina. It is premature to consider the suggestion of Dr. Meyer that new fundus lesions may indicate exacerbation of infection and the need for reinstitution of antibiotic therapy.

FRANCIS D. PIEN
Honolulu, Hawaii

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3. Bently, D.: *Staphylococcus epidermidis*. In Mandell, G., Douglas, R., and Bennett, J. (eds.): Principles and Practice of Infectious Diseases. New York, John Wiley and Sons, 1979, pp. 1554-1556.

Reply

Editor:

All patients in this series had the diagnosis of septicemia made by the Infectious Disease Service and had two or more positive blood cultures for the stated microorganisms. Although not reported, I examined the fundi of approximately 25 nonseptic adult patients on the medical service who did not have ocular disease, hypertension, diabetes mellitus, blood dyscrasias, or connective tissue disease. No fundus lesions were observed with direct or indirect ophthalmoscopy in these patients.

Previous investigators have demonstrated the association of fundus lesions in patients with nonendocarditis septicemia as referenced in the paper. In my study, one patient (Case 15) developed a new fundus lesion during a recurrent episode of spiking fevers. This new lesion was in the periphery near the equator and was clearly visible with indirect ophthalmoscopy. This lesion would be extremely difficult to detect with a direct ophthalmoscope. Since some of the fundus lesions observed in this study were subtle, the dilated fundus examination should be done by an ophthalmologist in any study of fundus lesions associated with systemic septicemia.

Staphylococcus epidermidis had been reported to cause subacute bacterial endocarditis in patients with and without valvular prostheses.[1,2] Additionally, *S. epidermidis* has been observed to cause postoperative wound infections with subsequent septicemia.[3] Previous investigators have found that *S. epidermidis* caused endophthalmitis in humans and in experimental animals.[4-6] In one recent report *S. epidermidis* was the most frequent isolate in human cases of endophthalmitis.[4] Thus, it appears *S. epidermidis* is more than just a rare cause of systemic and ocular infections.

SANFORD M. MEYERS, M.D.
Denver, Colorado

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Diagnostic Techniques in Angle-Closure Glaucoma

Editor:

I read with interest the article, "A comparison of diagnostic techniques in angle-closure glaucoma," by D. G. Campbell (Am. J. Ophthalmol. 88:197, 1979). In general, I agree with the findings, but Dr. Campbell mentioned that the Goldmann goniolens used in his study was of the three-mirror variety. (He did not indicate if it was the large or small version.) Becker[1] pointed out that this particular lens is not well suited for evaluating narrow chamber angles. The large corneal contact surface and the more peripheral position of the mirror make evaluation of narrow angles difficult. The smaller one- or two-mirror Goldmann goniolenses are a better tool for evaluating the angle, although perhaps they do not provide as much information as pressure-gonioscopy with the Zeiss lens.

RONALD C. RICHTER, M.D.
Baltimore, Maryland

Reference

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Lysozyme Content of Tears

Editor:

We recently read the article, "Lysozyme content of tears in patients with Sjögren's syndrome and rheumatoid arthritis," by R. Avisar and associates (Am. J. Ophthalmol. 87:148, 1979), in which our work[1] was quoted, and we wish to comment as follows:

When collecting tear fluid by absorption on to filter paper disks it is necessary to weigh the disk before and afterward to measure the volume collected. We found[1] that the volume collected by a wet disk can vary as much as threefold.

The tear lysozyme concentration given for normals, from 2,500 to 10,000 μg uncalibrated hen egg lysozyme per milliliter, was read from a difference in the zone sizes on their lysozyme plates of only 1.5 mm (15.0 to 16.5 mm). Furthermore a linear relationship could not be obtained with their standards over this range (see Figure 1). On their standard curve, the distance between the actual point obtained from the 10,000 μg/ml standard and the theoretical point assumed was an additional 0.6 mm, which can be considered equivalent to an error of 40% when compared to the range of 1.5 mm.

Dr. Avisar and associates used different batches of lysozyme plates, which can result in variation of results, especially when standards are not used on every plate.[2]

We find, as have others,[3] that a linear decrease in concentration of tear lysozyme occurs in normal volunteers with an increase in age from 20 years. Etches and associates[2] found that an increasing concentration of lysozyme occurred in tear fluid from pre-term to full-term babies. We doubt if Dr. Avisar's method was sufficiently accurate to detect a twofold difference in the mean titer of tear lysozyme concentration between 20- and 80-year-old normal volunteers.

Dr. Avisar and associates quote us[1] as finding a decreased titer of tear lysozyme in one of six patients with keratoconjunctivitis sicca. However, in Table 2 we stated that of six patients with keratoconjunctivitis sicca syndrome, four had low concentrations of tear lysozyme in both eyes, and two had low concentrations in one eye with marginal results in the other. There was no conflict, as suggested, in our results. In agreement with similar findings by others,[4,5] we suggested that the tear lysozyme concentration could be used as an index of lacrimal gland function and in the diagnosis of the syndrome.

We have since reported low concentrations of tear lysozyme obtained from patients with practolol-induced oculomucocutaneous syndrome.[6] We have now found low concentrations of tear lysozyme in 29 patients with keratoconjunctivitis sicca, as compared with 131 normals and controls with autoimmune disease. We have found low values in six of 18 patients with possible dry eyes, associated with particulate mucus in the tear film. All our results are age-adjusted and expressed as the tear-lysozyme ratio; a value less than 1.0 suggests the keratoconjunctivitis sicca syndrome.

D. V. SEAL, M. B.
Southampton, England

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Reply

Editor:

We found the bacteriologic method of assay of lysozyme in tears used to be the most suitable method for a screening test, though curves obtained by bacteriologic method of assay were almost not linear. We used the same batch of lysozyme for all the plates, and for every batch plate we used a standard.

The relationship of age and lysozyme content of tears by different analytic techniques showed no age effect.[1-3] Figure 3, which showed the effect of age on human tear lysozyme concentration reported by Pietsch[3] showed that increasing age only slightly affects the enzyme level in tears.

We incorrectly cited the results of the report of Mackie and Seal.[4] Instead of one of six, five of six patients were found to have decreased titer of lysozyme in tears. We have now found that bromehexine (Solvex) increased tear flow in 70% of 36 patients with keratoconjunctivitis sicca in whom lysozyme tear content also was increased.

R. AVISAR, M.D.
AND
H. SAVIR, M.D.
Petah-Tiqvah, Israel

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BOOK REVIEWS

Textbook and Atlas of Slit-Lamp Microscopy of the Living Eye, Volume 2. Lens and Zonule. By Alfred Vogt.

Translated by Frederick C. Blodi. Bonn, Wayenborgh Publishers, 1979. Hardcover, 422 pages, introduction, table of contents, bibliography, index, over 400 color figures. $342

In 1911, Dr. Gullstrand demonstrated a model of his slit lamp. This incidentally was the same year that he received the Nobel Prize, the first ophthalmologist to be so honored. Various modifications were made over the next few years but the major change occured in 1920 when Vogt used the slit as a stop to regulate the size of the beam. Thus he introduced the optical section. This great advance was followed within a year by publication of his Atlas der Spaltlampen Mikroscopie. This text described his apparatus, the technique for the use of the slit lamp, and the appearance of normal and diseased cornea and anterior chamber. Volume 2 appeared in 1931 and was devoted essentially to the lens and the zonule of Zinn. In 1942, Volume 3 was published. Previously only this volume was available in English. The translator is not given in the copy available to me.

For the first time Volume 2, devoted to the lens and zonule, is available in an English translation by Frederick Blodi. This is a beautiful book and it is astonishing to look through and realize that the observations and drawings were made with a slit lamp that we would consider primitive today. The illumination and the microscope were not parfocal, the light source was much poorer than now available, and a good fixation system was not developed. Nevertheless the drawings are of amazing clarity and accuracy. There is little that has been described in the lens which is not profusely illustrated and written about in this volume. When this volume was originally published there was little information on cause, and therefore, morphology was everything. Hence, a great deal of space is devoted to the different types of congenital cataracts. Descriptions of most of the disease processes include a case report. The illustrations are of superb clarity and color and are apparently taken from the original plates. A small section is devoted to the zonule, and it is humbling to read the description of hereditary spherophakia 20 years before the Marchesoni syndrome was described.

The question arises as to who should purchase this book. It is obviously completely outside the price range of the average house officer, and yet this is the person who would benefit most from reading about the variations in the normal lens and from the realization that congenital opacities come in an enormous variety of configurations and that not every lens opacity is acquired. I suggest that house officers urge their department directors to buy this book for the program library. I urge those more affluent practitioners who would like to hold a piece of the history of ophthalmology in their hands to purchase this for their personal libraries since even a casual glance at the photographs will be not only instructive but cause one to reflect on how much can be done with little. The greatest technologic advance remains the eye of the careful observer.

A few minor irritations include misspellings and germanisms and particularly the omission of the second "h" in words beginning with "ophthalmo." I hope Dr. Blodi will correct these in the second edition of this translation and will add a translator's preface on Dr. Vogt and the history of his atlases.

DAVID SHOCH

The Influence of Ocular Light Perception on Metabolism in Man and in Animal. By Fritz Hollwich. New York, Springer-Verlag, 1979. Hardcover, 129 pages, table of contents, bibliography,

subject index, 59 black and white figures. $37.50

This book is interesting for its informational content as well as for its Victorian style, which is manifest by the frequent citing of erudite quotations, mainly from Goethe. Professor Hollwich is a professor at the University of Muenster, and the book is translated from German. It deals with a seldom explored topic, the visual influences on metabolic activity, mediated by axons that branch from the optic nerve and ultimately terminate in the hypothalamus. Hollwich coins the term "energetic" portion of the optic nerve to distinguish these axons from the larger portion mediating conscious visual experience. These energetic signals affect circadian rhythms of autonomic and endocrine nature, involving organs as the pineal, pituitary, thyroid, adrenal, and the like. The book centers on the author's empiric studies of the effects of blindness on various metabolic rhythms in man. It is a short book (97 pages of text), barely beyond the level of a good doctoral thesis. Throughout, the beneficial effects of natural as opposed to artificial light are acclaimed with the zeal of a consultant to an Alpine sanitarium. A beneficial effect never considered, however, is that light reduces the leak to Na+ of vertebrate photoreceptors, and thereby eases their metabolic demands for energy. This is something possibly beneficial to these organelles, perhaps to the more genetically deficient ones. It is in such insights into cell biology that this book is most deficient; but as Goethe says, "Wo viel Licht ist, ist starker Schatten."

P. GOURAS

Glaucoma, 2nd ed. By Paul A. Chandler and W. Morton Grant. Philadelphia, Lea and Febiger, 1979. Hardcover, 381 pages, preface, index, 16 black and white figures. $26

There is no better book on glaucoma. The authors have fulfilled the aims stated in the Preface: "Our intent is merely to provide a practical guide for recognition and modern treatment of the various forms of glaucoma and for the solution of the problems encountered clinically."

The superb conversational didactic style, sprinkled with case examples, makes for easy and instructive reading. The content represents a most thorough and thoughtful analysis of clinical management based on the authors' own astute clinical observations and the published reports, with which the authors are exhaustively familiar. The reader is provided with unexcelled clinical wisdom and judgment based on all of the available information. One can, however, find points to argue. For example, just as the authors cannot understand why operating room gonioscopy has not been found valuable by many ophthalmologists, I do not understand why the authors have not discovered the value of good visual field examinations in the management of open-angle glaucoma. Other similar topics are open to debate or are subject to individual preferences. However, all subjects are treated fairly, opinions are identified as such, and it is hard to find judgments of the authors that one would consider unreasonable. Indeed, there are only a few with which one could reasonably disagree.

Compared to the competing textbooks devoted to glaucoma, this text contains little discussion of anatomy, physiology or pathophysiology, except where it bears directly on a particular clinical problem. This textbook is thus not an encyclopedia of facts whether or not they have clinical relevance. This approach contributes to the readability for the majority of ophthalmologists, whose rightful interest is in the current practical management of their patients.

For the scholar, who may want to

explore the basis for factual statements or to challenge them, there are only selected bibliographic citations (but more than in the first edition). Since exhaustive bibliographies are available elsewhere, this seems appropriate for a didactic book. Moreover, one would have to look long and hard to find any facts that are omitted, misquoted, misinterpreted, or stated without a valid basis by the authors.

This textbook has only one possible deficiency—the sparsity of illustration. The written descriptions are so lucid, however, that this may not be a major deficiency. Nevertheless, a few more illustrations might have clarified certain points for some readers.

DOUGLAS R. ANDERSON

Perimetric Standards and Perimetric Glossary of the International Council of Ophthalmology. By J. M. Enoch, E. Aulhorn, A. Dubois-Poulsen, F. Fankhauser, A. Friedmann, E. Greve, H. Harms, and G. Verriest. The Hague, W. Junk Publishers, 1979. Hardcover, 133 pages, table of contents, 2 black and white figures.

This small monograph is divided into two parts. A short introductory section gives the specifications for perimetry. It is suggested, for example, that photometric specifications be in candelas/m^2 and that background be no less than 10 candelas/m^2. Ideally, the target should be specified in terms of the solid angle subtended at the center of the entrance pupil of the eye and measured in steradians. Since this is not widely used the authors suggest as a substitute the number of degrees of arc at a specific test distance in millimeters. Although the diameter of the target in millimeters at a specific distance is also acceptable it is less to be desired than the previous unit. For static perimetry a duration of somewhere between 100 and 250 msec is necessary although this will obviously vary with the intensity of the luminance of the target. For a moving or kinetic target the most important point is stability of the rate of movement. The second half of this monograph lists 500 terms that are used in perimetry and gives these first in English and then their equivalents in French, German, Spanish, Russian, Italian, Swedish, Dutch, Polish, and Japanese. This glossary should help to standardize international terminology.

DAVID SHOCH

SYMPOSIA

Modern Problems in Ophthalmology. New Aspects of Vitreoretinopathology, Volume 20. Edited by E. W. D. Norton, C. Gailloud, N. Ducrey, and M. Gonvers. Basil, S. Karger AG, 1979. Hardcover, 440 pages, 183 black and white figures, 1 color plate. $170

I. Spontaneous primary detachment of the choroid
Secondary post-operative detachment of the choroid
II. Latest advances in the diagnosis of chorio-retinal diseases
Other advances in chorio-retinal surgery
III. Vitreous surgery in the treatment of intra-ocular foreign bodies
Vitreous surgery in the treatment of giant retinal tears (over 180°)
IV. Functional results in retinal detachment surgery
Prevention and correction of postoperative muscular disturbances
V. Treatment of the proliferative diabetic retinopathy
Treatment of non-diabetic vascular chorio-retinal diseases

Advances in Ophthalmology Anti-Herpesvirus Chemotherapy: Experimental and Clinical Aspects. Edited by K. K. Gauri. Basil, S. Karger AG, 1979. Hardcover, 300 pages, table of contents, preface, foreword, 87 black and white figures. $97.25

PRUSOFF, W. H., CHEN, M. S., FISCHER, P. H., LIN T.-S., SHIAU, G. T., AND SCHINAZI, R. F.: Role of nucleosides in virus and cancer chemotherapy

LENNARTZ, H.: Diagnosis of herpes simplex

NASEMANN, T.: Pathogenesis of herpes simplex infection of the skin and its relationship to the eye

NAHMIAS, A., VISINTINE, A., HANEY, M., STANWICK, T., LEE, F., AND CAVANAGH, D.: Isolation, quantitation, and electron microscopic detection of virus from tears in human herpetic keratitis-relation to antiviral therapy

SCHWÖBEL, W., STREISSLE, G., AND KIEFER, G.: Evaluation of antiherpetic drugs by in vitro assays

STREISSLE, G.: Comparative evaluation of antiherpetic drugs in animal experiments

LERCHE, W., VON DOMARUS, D., HANKE, C., MAASS, C., AND GAURI, K. K.: Electron microscopic studies following treatment with 5-ethyl-2′-deoxyuridine

NEWTON, A. A.: Inhibitors of prostaglandin synthesis as inhibitors of herpes simplex virus replication

GAURI, K. K., AND ALBRECHT, C.: Relative potencies of ethyldeoxyuridine and EdU-monophosphate in type 1 herpes keratitis in rabbits

WERNER, G. T., METZGER, E., AND SAUER, O.: Adenine arabinoside monophosphate in experimental vaccinia virus infections

PAVAN-LANGSTON, D.: Current trends in therapy of ocular herpes simplex: experimental and clinical studies

ALBERT, D. M., PERCY, D. H., PULIAFITO, C. A., FRITSCH, E., PAVAN-LANGSTON, D., LIN, T.-S., WARD, D. C., AND PRUSOFF, W. H.: AIU: An antiherpetic drug with low neonatal toxicity in mice

WOLENSAK, J.: Herpes simplex of the eye and possibilities of its therapeutic control

MARTENET, A.-C.: Experiences with iododeoxycytidine in the treatment of ocular herpes simplex infections

BIGAR, F.: Clinical experiences with trifluorothymidine in herpes simplex keratitis

EGERER, I.: Combined therapy (corneal abrasion and vidarabin ointment) in the treatment of herpes simplex kertititis

WASSILEW, S. W.: Treatment of herpes simplex of the skin. Critical evaluation of antiherpetic drugs with reference to relative potency on the eye

ELZE, K.-L.: Ten years of clinical experiences with ethyldeoxyuridine

DAVIS, W. B., OAKES, J. E., VACIK, J. P., REBERT, R. R., AND TAYLOR, J. A.: 5-ethyl-2′- deoxyuridine as a systemic agent for treatment of herpes simplex virus encephalitis. Comparison of effects in a normal and immunosuppressed murine model

GAURI, K. K.: Anti-herpesvirus polychemotherapy

GENTRY, G., MCGOWAN, J., BARNETT, J., NEVINS, R., AND ALLEN, G.: Arabinosylthymine, a selective inhibitor of herpesvirus replication: Current status of in vivo studies

CHENG, Y-C., HOFFMANN, P. J., OSTRANDER, M., GRILL, S., CARADONNA, S., TSOU, J., CHEN, J.-Y., GALLAGHER, M. R., AND FLANAGAN, T. D.: Properties of herpesvirus-specific thymidine kinase, DNA polymerase and DNase and their implication in the development of specific antiherpes agents

MULLER, W. E. G., AND FALKE, D.: Cellular and herpesvirus polymerases: Their significance for chemotherapy

FALKE, D., MOSER, H., LINK, D., AND MULLER, W. E. G.: The effects of a- and b-D-arabinosyladenosine and b-D-arabinosylthymine on the synthesis of HSV types 1- and 2-infected cells

DE CLERCQ, E.: 5-substituted 2′-deoxyuridines which selectively inhibit herpes simplex virus replication

AEBERSOLD, P. M.: Relative mutagenicity of nucleoside virostatic drugs in Chinese hamster ovary cells

KOCH, G., WARNECKE, G., KUHNE, J., AND BILELLO, J. A.: Effect of base analogs upon the induction of differentiation in friend erythroleukemia cells

CHANDRA, P.: Viruses and human cancer: A puzzle with a few missing pieces

ROLLINGHOFF, M., PFIZENMAIER, K., FALKE, D., AND WAGNER, H.: T Cell-mediated cytotoxic immune response to HSV infection and its modification due to antimetabolites

GAURI, K. K., PRESSLER, K., SCHENK, K. D., SCHEFFLER, G., AND REBLING, R.: Antiviral activity of compounds modified from the imidazolidinone deriviative impacarzinum

NEWTON, A. A.: Inhibition of the replication of herpes viruses by phosphonoacetate and related compounds

HELGSTRAND, E., OBERG, B., AND ALENIUS, S.: Experimental studies on the antiherpetic agent phosphonoformic acid

VACIK, J. P., DAVIS, W. B., KELLING, C. S., SCHERMEISTER, L. J., AND SCHIPPER, I. A.: Current status of studies on the antiviral activity of a water-soluble extract from narcissus bulb against herpes viruses

WHILEY, R. J., AND ALFORD, C. A.: Developmental aspects of adenine arabinoside for parenteral therapy of human herpesvirus infections

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Acta Neurologica Scandinavica

VISUAL EVOKED POTENTIAL IN PATIENTS WITH CEREBRAL ASTHENOPIA. Gulmann, N. C., Hammerberg, P. E., Jensen, L. B., Sommerbeck, K. W., and Orbaek, K. (Dept. Clin. Neurophysiology, Glostrup Hosp., Denmark). Acta Neurol. Scand. 59:324, 1979.

Cerebral asthenopia is a condition in which patients complain that they see changes of different kinds a few seconds after fixation of a stationary object. The object may change form, contour, position or it may appear to move and there may be monocular diplopia. These changes of a central origin are not due to any abnormality in the eye or difficulty in fixation. Each patient usually describes the disturbances with marked regularity in repeated test situations so that it appears that the asthenopic symptoms are due to disturbances at a rather primitive level in the cerebral organization of visual perception. An objective correlate of this symptom so far has never been demonstrated. The authors recorded the visual evoked potential in ten patients with cerebral asthenopia and 20 normal subjects. There was no difference of latency in the two groups but the amplitude of the most prominent component was significantly reduced in the patients. The amplitude difference is probably modal specific and suggests involvement of the visual cortex. However, because of the great overlap between amplitudes in asthenopic patients and control subjects the visual evoked potential is unsuitable as a diagnostic tool for this entity. (1 figure, 3 tables, 11 references)—David Shoch

Acta Ophthalmologica

REFSUM'S DISEASE: EYE MANIFESTATIONS IN A PATIENT TREATED WITH LOW PHYTOL LOW PHYTANIC ACID DIET. Hansen, E., Bachen, N.I., and Flage, T. (Dept. Ophthalmol., Rikshospitalet, The National Hospital, Univ. Oslo, Norway). Acta Ophthalmol. 57:899, 1979.

Refsum's disease is a hereditary disorder of lipid metabolism in which there is an absence of phytanic acid ∝-hydrolase, an enzyme that is responsible for the first step of phytanic acid degradation. The cardinal eye symptoms are night blindness, retinal pigmentary degeneration and constriction of visual fields. The patient reported here is a 39-year-old male who had a diagnosis of Refsum's disease made at the age of seven. He has been on a low phytol low phytanic acid diet for the last 13 years. In the last seven years there has been minimal or no progression of the visual findings. The fields have not constricted in that period and all cone mechanisms are functioning at the normal level. The ERG shows only moderate abnormality. The authors feel that the special diet reduced the rapidity of the progress of this disease. In a sense this is one type of "retinitis pigmentosa" that is treatable. (7 figures, 23 references)—David Shoch

Albrecht von Graefes Archiv für Klinische und Experimentelle Ophthalmologie

HISTOLOGICAL AND ULTRASTRUCTURAL STUDIES OF THE CORNEA IN MAROTEAUX-LAMY SYNDROME. Süveges, I. (Dept. Ophthalmol., Univ. Med., Debrecen, Hungary). Albrecht von Graefes Arch. Klin. Ophthalmol. 212:29, 1979.

The Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI) belongs to the lysosomal storage diseases. It is probably the result of the lack of the lysosomal enzyme arylsulfatase-B causing a disturbance in the catabolism of the sulfated glycosaminoglycans which results in an elevated urinary excretion of chondroitin-4-sulfate. The clinical characteristics greatly resemble Hurler's disease except that the children usually have normal intellectual development. By means of electron microscopy three cell types have been found in the stroma which may show, besides the storage of the accumulated glycosaminoglycans, the morphologic signs of the pathologic enzyme-

substrate connection. Considering the presence of the lipidlike material, the question arises whether the Maroteaux-Lamy syndrome belongs to mucolipidoses. (8 figures, 11 references)—David Shoch

Anesthesiology

PLASMA CATECHOLAMINE LEVELS DURING LOCAL ANESTHESIA FOR CATARACT OPERATIONS. Donlon, J. V., and Moss, J. (Anesthesia Ser., Massachusetts Eye and Ear Infirm., Harvard Med. School, Boston, Mass.). Anesthesiology 51:471, 1979.

The source of catecholamines in the blood during cataract surgery is either the epinephrine that is added to the anesthetic for akinesia and anesthesia or endogenously produced norepinephrine in response to stress, pain and anxiety. The authors show that with the usual dose of epinephrine given which is about 0.06 mg there is very little increase in the circulating catecholamines and that in the patients they studied there were no evidences of any untoward effect on the heart. The New York Heart Association recommends an upper limit of 0.2 mg of epinephrine and this level would only be reached with enormous volumes of injected material.

On the other hand there were rather marked increases of endogenous catecholamines with anxiety, pain and stress. Therefore, it is essential that patients fears, anxieties and pain be allayed as much as possible either by psychologic means or with use of appropriate medication. Untoward effects from increased catecholamines are much more likely to arise from endogenously produced norepinephrine than from exogenously introduced epinephrine in anesthetic solutions. (2 tables, 13 references)—David Shoch

Annals of Internal Medicine

FORMED VISUAL HALLUCINATIONS AS DIGITALIS TOXICITY. Volpe, B. T., and Soave, R. (Cornell Univ. Med. Ctr., New York, N.Y.). Ann. Intern. Med. 91:865, 1979.

The visual toxicity of digitalis is usually reported as changes in the color values of objects. Green vision is the most common complaint but yellow vision and purple vision have also been reported. In this paper three patients are described in whom the visual toxicity took the form of hallucinations. The objects seen varied from butterflies to bird houses to soldiers to familiar household objects. Investigation of other organ systems failed to reveal any abnormalities. In all three cases the hallucinations ceased when the serum digoxin level fell below 2 ng/ml. Digitalis toxicity should be considered in the differential diagnosis of patients with formed visual hallucinations even in the absence of well-recognized cardiac and gastrointestinal side effects. (10 references)—David Shoch

Archives of Internal Medicine

RETINAL ARTERIOLAR CHANGES AS AN INDICATOR OF CORONARY ARTERY DISEASE. Michelson, E. L., Morganroth, J., Nichols, C. W., and MacVaugh, H. (Cardiovascular Sec., Depts. Med. and Ophthalmol., Univ. Pennsylvania, Philadelphia, Pa.). Arch. Intern. Med. 139:1139, 1979.

Funduscopic examination was performed in 70 nondiabetic, nonhypertensive patients without valvular heart disease undergoing coronary angiography for evaluation of chest pain syndromes to determine if retinal arteriolar changes could reliably predict presence of coronary artery disease. Retinal arteriolar changes were graded with respect to light reflex, vessel caliber, arteriovenous crossing defects, and vessel tortuosity without knowledge of angiographic findings. Each coronary vessel was graded with respect to its most occlusive lesion by angiography; coronary index was derived for each patient without knowledge of eye findings. Abnormal light reflex changes were the most sensitive indicators of presence and extent of coronary artery disease. Abnormal vessel tortuosity and decreased caliber were less sensitive but more specific; their presence also suggested more extensive coronary lesions. Thus, funduscopic examination demonstrating specific retinal arteriolar lesions may indicate presence of coronary artery disease and may correlate with

extent of lesions in selected patients. (1 figure, 1 table, 10 references)—Authors' abstract

Archives of Neurology

AMYOTROPHIC LATERAL SCLEROSIS WITH OPHTHALMOPLEGIA: A CLINICOPATHOLOGIC STUDY. Harvey, D. G., Torack, R. M., and Rosenbaum, H. E. (Dept. Neurol., Washington Univ. School of Med., St. Louis, Mo.). Arch. Neurol. 36:615, 1979.

Ophthalmoplegia is rarely observed in patients with amyotrophic lateral sclerosis. The authors describe a patient with amyotrophic lateral sclerosis in whom ophthalmoplegia, initially appearing midway in her course, progressed to total paralysis of extraocular movements by the time of death. In addition to the usual postmortem findings in the brain stem and spinal cord, there was extensive neuronal loss and gliosis involving the caudal portions of the dorsal and intermediate components of the oculomotor nuclei, the caudal part of the trochlear nuclei, and the abducens nuclei. This represents the first detailed report of the findings in the nuclei of cranial nerves III, IV, and VI in a patient with amyotrophic lateral sclerosis and ophthalmoplegia. (7 figures, 12 references)—Authors' abstract

UNILATERAL VISUAL LOSS IN BRIGHT LIGHT: AN UNUSUAL SYMPTOM OF CAROTID ARTERY OCCLUSIVE DISEASE. Furlan, A. J., Whisnant, J. P., and Kearns, T. P. (Depts. Neurol. and Ophthalmol., Mayo Clinic and Mayo Foundation, Rochester, Minn.). Arch. Neurol. 36:675, 1979.

Five patients with carotid artery occlusive disease had unilateral visual loss in bright light. All five had reduced retinal artery pressure on the side of the visual loss, and arteriograms showed either an occlusive or a high-grade stenosis of the ipsilateral internal carotid artery. Unilateral visual loss in bright light may indicate ipsilateral carotid artery occlusive disease and may reflect the inability of borderline circulation to sustain the increased retinal metabolic activity associated with exposure to bright light. (11 references)—Authors' abstract

RETINAL HEMORRHAGES: ITS SIGNIFICANCE IN 100 PATIENTS WITH ACUTE ENCEPHALOPATHY OF UNKNOWN CAUSE. Keane, J. R. (Dept. Neurol., Univ. Southern California Med. Ctr., Los Angeles, Calif.). Arch. Neurol. 36:691, 1979.

A total of 94 patients had subarachnoid hemorrhage and it was strongly suspected in the remaining six patients. Acute encephalopathy associated with independent ocular hemorrhage due to hypoxia, multiple emboli, or bleeding tendencies was not a diagnostic problem during this study. Aneurysms occurred in 64 patients (combined with vascular malformations in four), isolated vascular malformations in four; "spontaneous" hematomas in 13, evidence of cryptic head trauma in six, hemorrhage from a glioblastoma in one, and no cause was identified in six patients. Retinal hemorrhages were more prominent ipsilateral to the site of intracranial bleeding. No single aneurysm location predominated and multiple aneurysms were common. The high mortality of 56% supports previous conclusions that retinal hemorrhages tend to accompany severe intracranial bleeding. (6 figures, 1 table, 12 references)—Author's abstract

Archives of Ophthalmology

OCULAR *Toxocara* IN SIBLINGS OF TWO FAMILIES. Pollard, Z. F. (Dept. Ophthalmol., Scottish Rite Hosp. for Crippled Children, Atlanta, Ga.). Arch. Ophthalmol. 97:2319, 1979.

Two children each of two families had severe loss of vision in one eye each. All four children were diagnosed as having *Toxocara* retinopathy and this clinical diagnosis was confirmed by the enzyme-linked immuno-sorbent assay (ELISA) test. Apparently this is the first report of involvement in more than one sibling in a family. This article suggests that when ocular *Toxocara* is found in a child every sibling in the family should be examined. (4 figures, 11 references)—David Shoch

HYALURONIC ACID VITREOUS SUBSTITUTE: A SIX-YEAR CLINICAL EVALUATION. Pruett, R. C., Schepens, C. L.,

and Swann, D. A. (Retina Associates and the Eye Research Inst. of Retina Foundation, Boston, Mass.). Arch. Ophthalmol. 97:2325, 1979.

Hyaluronic acid vitreous substitute (HYVISC) was used during 347 operations performed on 294 eyes of 286 patients. It was injected intraocularly in 266 operations (73 scleral bucklings, 175 open-sky vitrectomies, among others) on eyes with complex retinal detachments that were considered inoperable by ordinary surgical techniques. During 81 closed vitrectomies, it was applied extraocularly between the surgical contact lens and the cornea. Hyaluronic acid was found to be well tolerated by human eyes. In eyes that had been given a poor prognosis, scleral buckling with hyaluronic acid tamponade produced reattachment in 16% of the eyes; open-sky vitrectomy, scleral buckling, and hyaluronic acid salvaged 18%. It also appeared helpful in the preservation of corneal epithelial integrity and clarity during closed vitrectomy. (6 figures, 7 references)—Authors' abstract

RETINAL FLUOROGRAPHY USING ORAL FLUORESCEIN. Kelley, J. S., and Kincaid, M. (Dept. Ophthalmol., Greater Baltimore Med. Ctr., Baltimore, Md.). Arch. Ophthalmol. 97:2331, 1979.

Intravenous fluorescein gives crisp sharp fluorescein angiograms and is therefore of great advantage when fine details of the vascular tree are required. However, frequently an angiogram is performed to determine whether there is a break in the barrier to fluorescein and whether a late leak will occur. This is particularly of interest in cases of cystoid macular edema and melanoma, for example. In such cases good quality angiograms may be obtained at the end of 15 or 30 minutes with the administration of oral fluorescein. The authors use a 1 g dose of fluorescein sodium in a sweetened and iced citrus drink. This is obviously a great advantage in children. (3 figures, 3 references)—David Shoch

Experimental Eye Research

LOSS OF CORNEAL SENSITIVITY WITH LID CLOSURE IN HUMANS. Millodot, M., and O'Leary, D. J. (Lab. Exp. Optometry, Univ. Wales Inst. of Sci. and Tech., Cardiff, U.K.). Exp. Eye Res. 29:417, 1979.

Corneal sensitivity and thickness were measured after various periods of eyelid closure in human subjects. The results showed a marked and progressive loss of corneal sensitivity and a small increase in corneal thickness. These findings are analogous to the changes known to occur in the acetylcholine content of the corneal epithelium. (2 figures, 23 references)—Authors' abstract

Laryngoscope

CONJUNCTIVAL APPROACH FOR LOWER LID BLEPHAROPLASTY. Maniglia, A. J. (Dept. Otolaryngol., Univ. Miami, Miami, Fla.). Laryngoscope 89:1869, 1979.

In the presence of fat pads in the lower eyelid without excess skin it is possible to repair these through the conjunctiva. This procedure is uncommon but has the advantage of leaving no scar on the skin surface. The incision is made on the conjunctival side just inferior to the tarsus and it avoids the possibility of ectropion. The author reports 15 patients on whom he has performed this procedure with no complications. (5 figures, 3 references)—David Shoch

New England Journal of Medicine

IATROGENIC NIGHT BLINDNESS AND KERATOCONJUNCTIVAL XEROSIS. Partamian, L. G., Sidrys, L. A., and Tripathi, R. C. (Univ. Chicago, Chicago, Il.). N. Engl. J. Med. 301:943, 1979.

A 51-year-old woman underwent a jejunoileal bypass procedure seven years prior and was now complaining of blurred vision and ocular irritation. Visual acuity was normal as were examination of the fundi and electroretinographic studies. Topical 1% rose bengal revealed diffuse staining of the cells of the conjunctival and corneal epithelium and occasional xerotic spots in the conjunctiva. A conjunctival biopsy showed irregularity of the epithelial thickness, acanthosis and inclusion of

keratohyaline granules. Dark adaptation studies revealed elevated thresholds in both eyes. It thus seems likely that in this patient the iatrogenic vitamin A deficiency was induced by a jejunoileal bypass and such patients should probably be placed on judicious doses of vitamin A and should have dark adaptation tests at intervals.—David Shoch

Ophthalmology

THE TREATMENT OF ANGLE NEOVASCULARIZATION WITH PANRETINAL PHOTOCOAGULATION. Jacobson, D. R., Murphy, R. P., and Rosenthal, A. R. (Div. Ophthalmol., Stanford Univ., Stanford, Calif.). Ophthalmol. 86:1270, 1979.

Thirty-two eyes in 28 patients with anterior chamber angle neovascularization were prospectively treated with panretinal photocoagulation. Of 17 eyes that had less than a 270 degree angle closure, with an intraocular pressure of less than 40 mm Hg prior to treatment, 16 showed complete disappearance of the angle neovascularization and stabilization of the peripheral anterior synechiae after treatment. None of the 15 patients who had angle closure of 270 degrees or greater, or an intraocular pressure of above 4 mm Hg, showed any significant improvement after treatment. These results suggest that panretinal photocoagulation offers a highly effective means of dealing with early and moderately advanced cases of angle neovascularization. (3 figures, 2 tables, 12 references)—Authors' abstract

SUPRATHRESHOLD STATIC PERIMETRY IN GLAUCOMA AND OTHER OPTIC NERVE DISEASE. Johnson, C. A., Keltner, J. L., and Balestrery, F. G. (Dept. Ophthalmol., Univ. California, Davis, Calif.). Ophthalmol. 86:1278, 1979.

Comparisons between automated suprathreshold static perimetry and manual kinetic perimetry were performed for 226 eyes with glaucoma or ocular hypertension, and 147 eyes with other optic nerve disease. Both techniques produced similar high detection rates for glaucomatous visual field defects, whereas suprathreshold static perimetry performed significantly better than kinetic testing in optic nerve disease other than glaucoma. It is concluded that automated suprathreshold static perimetry is an excellent quantitative screening technique for detecting visual field defects. (7 figures, 7 references)—Authors' abstract

THE TREATMENT OF ORBITAL RHABDOMYOSARCOMA WITH IRRADIATION AND CHEMOTHERAPY. Abramson, D. H., Ellsworth, R. M., Tretter, P., Wolff, J. A., and Kitchin, F. D. (Columbia-Presbyterian Med. Ctr., New York, N.Y.). Ophthalmol. 86:1330, 1979.

Fifty-eight patients with orbital rhabdomyosarcoma were treated with irradiation alone (25) or irradiation and chemotherapy (33) with follow-ups of six months to 14 years (mean 5.2 yr). At present, 74% are alive and 26% have died. Local control of the tumor was accomplished in 91% of cases. When local sinuses were invaded the survival rate was 55%. Chemotherapy appears to be of greatest value when disease is limited to the orbit. Irradiation or irradiation and chemotherapy should now be the treatment of choice for orbital rhabdomyosarcoma. (8 references)—Authors' abstract

DIAGNOSIS AND MANAGEMENT OF CANCER METASTATIC TO THE UVEA: A STUDY OF 70 CASES. Stephens, R. F., and Shields, J. A. (Oncology Unit, Retina Ser., Wills Eye Hosp., Philadelphia, Pa.). Ophthalmol. 86:1336, 1979.

Although metastatic cancer to the uvea is reported to be the most common intraocular malignancy, most ophthalmologists have had little experience with its diagnosis and treatment. This report describes the authors experience with the diagnosis and management of 70 patients with metastatic cancer to the uvea. Many patients were evaluated with modern diagnostic modalities such as fluorescein angiography, ultrasonography, and the ^{32}P test when indicated.

Thirty-one percent of patients had no history of previous malignancy, and the ocular complaints represented the first symptoms of systemic cancer. The ocular malignancy often simulated better-known ophthalmic entities, and the referring diagnosis was correct in only

38% of cases. This series, therefore, reflects the clinical problem confronting the practicing ophthalmologist.

About one-half of the patients were treated with external beam irradiation to the involved eye(s), which often resulted in dramatic resolution of the tumor and visual return. Other patients had either no treatment, chemotherapy, or enucleation in selected instances.

This report, based upon experience with these 70 cases, is designed to prepare guidelines for the ophthalmologist in the diagnosis and managment of patients with cancer metastatic to the uvea. (7 figures, 11 tables, 25 references)—Authors' abstract

Pain

CORNEAL PAIN EVOKED BY THERMAL STIMULATION. Beuerman, R. W., and Tanelian, D. L., (Div. Ophthalmol., Stanford Univ. Med. Ctr., Stanford, Calif.). Pain 7:1, 1979.

The thermal sensitivities of the eyelid and cornea were compared using an automated apparatus to produce stimulus pulses of known magnitude and duration over the range 33-45°C. Subjects reported only temperature sensation when the skin of the upper eyelid was tested; however, corneal stimulation in the same subject was always perceived as a painful stimulus. This was true throughout the range of temperatures. All applications were made to the center of the cornea and although the subjects could identify these as being in the cornea and being painful they could not identify which area of the cornea was being stimulated. This would indicate a great amont of overlap of nerve endings throughout the cornea and that further the cornea seems to have as its only response to stimulation, a sensation of pain. (4 figures, 3 tables, 31 references)—David Shoch

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FRANK W. NEWELL, M.D.
Editor-in-Chief
AMERICAN JOURNAL OF OPHTHALMOLOGY

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

Send News Items double-spaced to News Editor, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

TUFTS UNIVERSITY SCHOOL OF MEDICINE: ORBITAL ANATOMY DISSECTION COURSE

Tufts University School of Medicine will hold an orbital anatomy dissection course May 2 and 3, 1980. For further information, write Mrs. Emelie Born, 136 Harrison Ave., Boston MA 02111.

CANADIAN IMPLANT ASSOCIATION: INTRAOCULAR LENS IMPLANTATION SEMINAR

A seminar on intraocular lens implantation will be held June 21, 1980, at St. Mary's Hospital in Montreal in cooperation with the Canadian Implant Association. For further information, write M. L. Kwitko, M.D., Program Chairman, 5591 Cote des Neiges Rd., Suite 1, Montreal, Canada H3T 1Y8.

UNIVERSITY OF ROCHESTER: STRABISMUS SYMPOSIUM

The University of Rochester will sponsor a strabismus symposium June 13 and 14, 1980, at the University of Rochester Medical Center, Rochester, New York. For further information, write the Office of Continuing Professional Education, University of Rochester Medical Center, 601 Elmwood Ave., Box 601, Rochester, NY 14642.

WALTER REED EIGHTH BIENNIAL POSTGRADUATE COURSE AND ALUMNI MEETING

The Walter Reed eighth biennial postgraduate course and alumni meeting will be held April 28-30, 1980. For further information, write Col. Floyd L. Wergeland, Jr., MC, Chief, Ophthalmology Service, Rm. 1F, NMTF, Walter Reed Army Medical Center, Washington, DC 20012.

KENTUCKY ACADEMY OF EYE PHYSICIANS AND SURGEONS: ANNUAL SPRING MEETING

The Kentucky Academy of Eye Physicians and Surgeons will hold its annual spring meeting April 11 and 12, 1980. For further information, write Sheldon B. Schiller, M.D., Secretary, Kentucky Academy of Eye Physicians and Surgeons, 3532 Ephraim McDowell Dr., Louisville, KY 40205.

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY: 1979–1980 OFFICERS

The 1979-1980 officers of the Minnesota Academy of Ophthalmology and Oto-Laryngology are as follows: Melvin Sigel, president; Harry S. Friedman, vice president-OPH; Arndt John Duvall III, vice president, OTO; and Martin G. Bruhl, secretary-treasurer.

UNIVERSITY OF IOWA: IOWA EYE ASSOCIATION ANNUAL MEETING

The Iowa Eye Association at the University of Iowa will hold its annual meeting May 15-17, 1980. For further information, write Thomas A. Weingeist, M.D., University of Iowa, University Hospitals, Iowa City, IA 52242.

PERSONALS

D. JACKSON COLEMAN

D. Jackson Coleman has been appointed ophthalmologist-in-chief of New York Hospital and chairman of the Department of Ophthalmology at Cornell University Medical College, New York City. Previously, Dr. Coleman was assistant professor of ophthalmology at Columbia University College of Physicians and Surgeons, New York.

J. TERRY ERNEST

J. Terry Ernest has been appointed chairman of the Department of Ophthalmology at the Indiana University School of Medicine in Indianapolis. Dr. Ernest had been professor of ophthalmology at the University of Wisconsin Medical School in Madison.

GEORGE O. WARING

George O. Waring received the Heed Award during the 1979 American Academy of Ophthalmology meeting in San Francisco. The award was pre-

sented by Frank W. Newell, chairman of the Board of Directors of the Heed Foundation. Dr. Waring received the award in recognition of his leadership and contributions in the field of ophthalmology. Dr. Waring is associate professor at Emory University. Former recipients of the Heed Award include Stuart I. Brown, Goodwin M. Breinin, Matthew D. Davis, J. Terry Ernest, Milton Flocks, Froncie Gutman, Eugene Helveston, William T. Hoyt, Philip Knapp, Paul R. Lichter, Harvey A. Lincoff, William Spencer, and William S. Tasman.

New Research Grants Awarded By The National Eye Institute
October 1, 1979, to December 31, 1979
Research Project Grants

Institution	Principal Investigator	Title of Project	Costs Awarded
Virginia Commonwealth University Richmond, Virginia	Ludwig I. Epstein	A reading aid for patients with macular blindness	$ 34,614
New York University New York, New York	Ira M. Goldstein	Inflammation due to prosthetic intraocular lenses	23,918
Technion-Israel Institute of Technology Haifa, Israel	Ido Perlman	Mechanisms of visual adaptation in the vertebrate eye	25,750
University of Texas Health Science Center Dallas, Texas	Barry A. Sokol	Photoreceptor responses to single photon absorptions	83,348
Eye and Ear Hospital of Pittsburgh Pittsburgh, Pennsylvania	Nirmala Sundar Raj	Characterization of corneal cell-surface antigens	85,678
University of California Santa Barbara, California	Steven K. Fisher	Studies on the developing and adult visual systems	38,157
Yale University New Haven, Connecticut	Joy Hirsch	Pattern recognition mechanisms in amblyopia	30,389

INSTRUCTIONS TO AUTHORS

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THE AMERICAN JOURNAL OF OPHTHALMOLOGY publishes original and timely articles dealing with clinical and basic ophthalmology. Every typescript submitted is evaluated by two or more scientific referees who recommend that the paper be (1) accepted as submitted, (2) returned for revision, or (3) rejected. Acceptance is determined by such factors as the originality, significance, and validity of the contribution; the suitability of the subject matter for subscribers of THE JOURNAL; and the editorial care with which the manuscript has been prepared. Manuscripts that require extensive editorial correction or mechanical preparation will be returned for that purpose.

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Submit an original and at least one duplicate copy of both the typescript and the figures. Xerographic duplicates of the typescript are preferred to carbon copies.

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1. Fuxe, K., and Jonsson, G.: The histochemical fluorescence method for the demonstration of catecholamines. Theory, practice and application. J. Histochem. Cytochem. 21:293, 1973.

2. Bjorklund, A., Flack, B., and Owman, C.: Fluorescence microscopic and microspectrofluorometric techniques for the cellular localization and characterization of biogenic amines. In Berson, S. A. (ed.): Methods in Investigative and Diagnostic Encocrinology, vol. 1. London, North-Holland Publishing Co., 1972, p. 318.

3. Duke-Elder, S., and Leigh, A. G.: Diseases of the Outer Eye. Cornea and Sclera. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 8, pt. 2. St. Louis, C. V. Mosby, 1965, pp. 811-856.

Abbreviations of periodicals are listed in Index Medicus: Am. J. Ophthalmol.; Surv. Ophthalmol.; Br. J. Ophthalmol; and the like. If there is any doubt about an abbreviation, the name of the publication should be spelled out completely.

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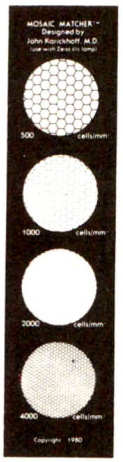

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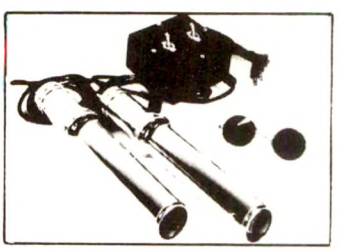

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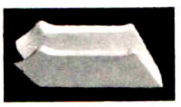

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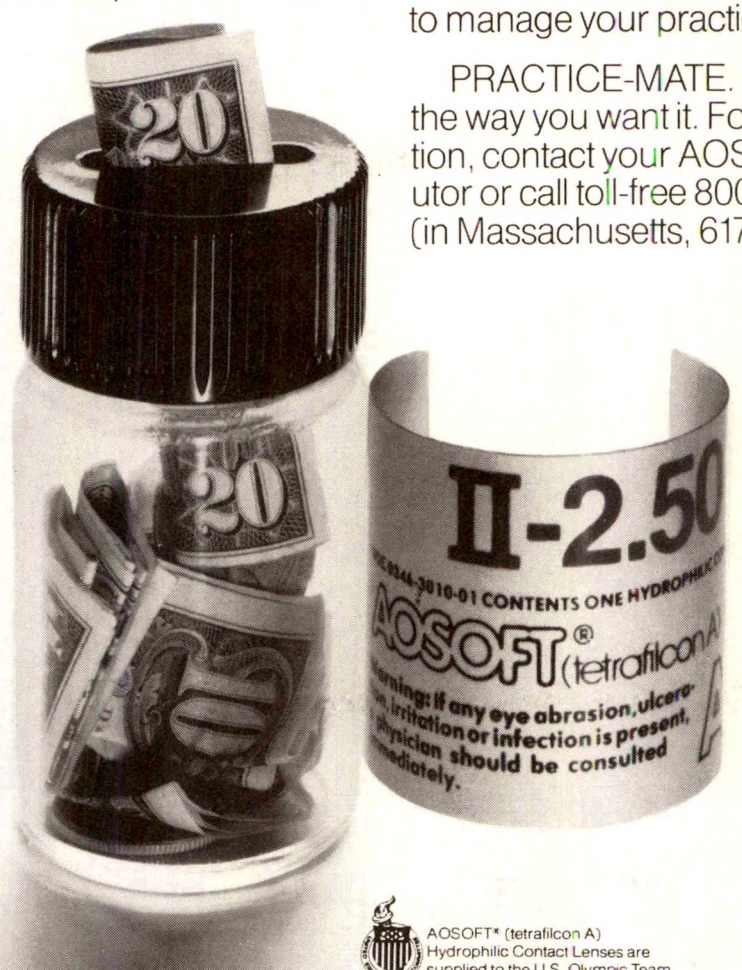

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Sponsored by
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For registration information:
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Cornell University Medical School
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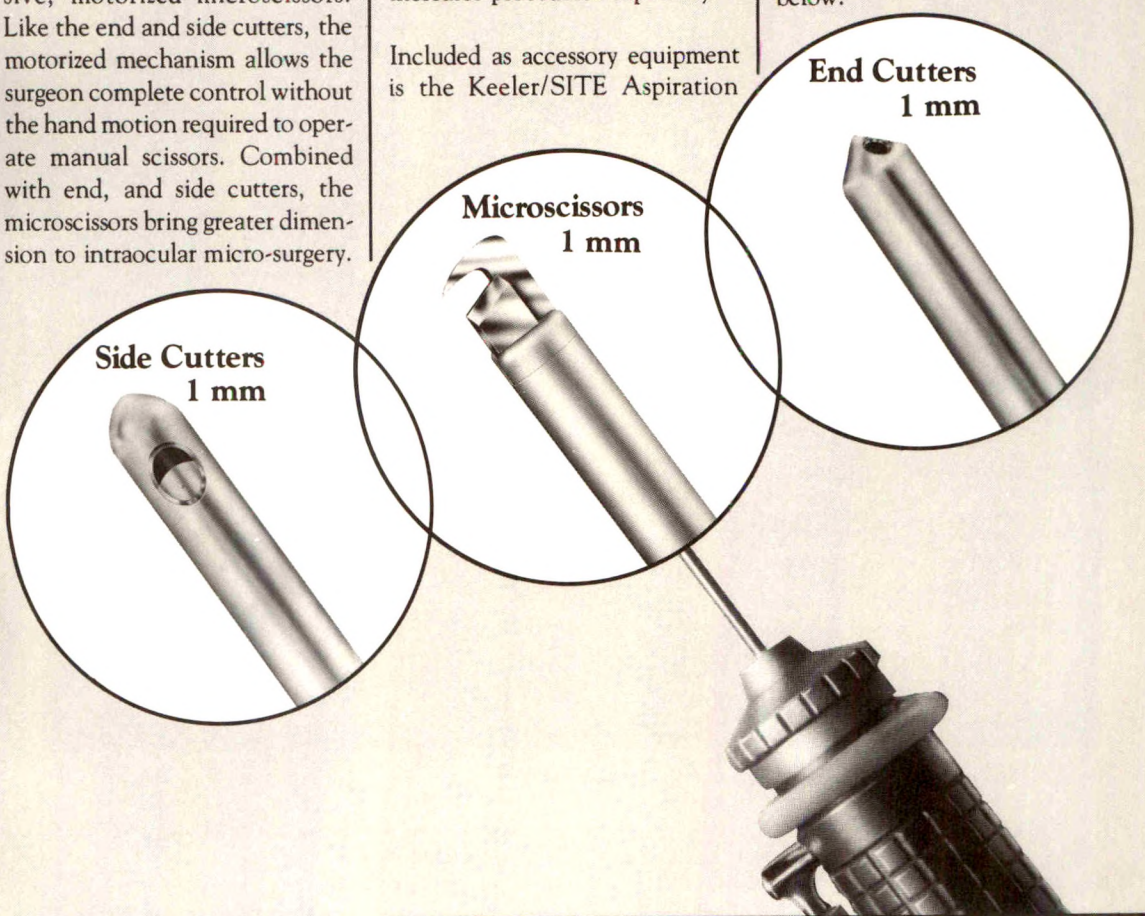

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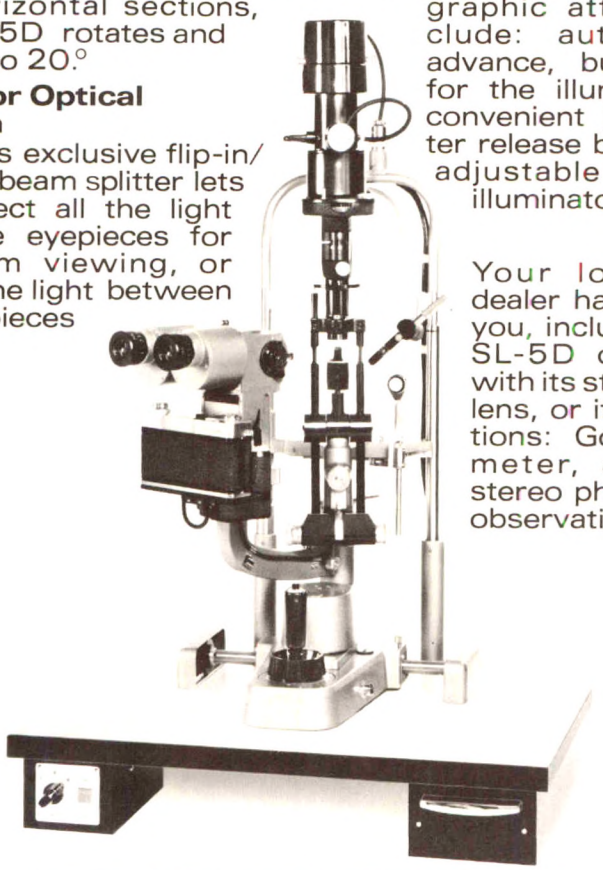

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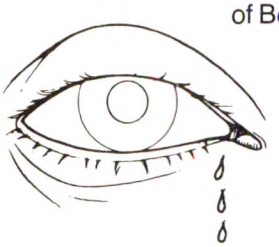

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INTRAOCULAR LENS IMPLANTATION UPDATE

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in cooperation with
The Canadian Implant Association (CIA)
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Speakers

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ANNOUNCEMENT
CALL FOR NOMINATIONS

1980 Award of Merit in Retina Research

The Retina Research Foundation, Houston, Texas, announces a call for nominations for the 1980 AWARD OF MERIT IN RETINA RESEARCH, to recognize a vision scientist whose work represents (a) single outstanding achievement in basic retina research or (b) a potentially significant contribution to new basic knowledge about the retina, its role in the visual process, and/or vitreoretinal diseases and disorders. President and Scientific Director of the Foundation is Alice McPherson, M.D., F.A.C.S., F.I.C.S.

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Nomination Procedure: The following must be submitted: (1) letter of nomination including brief statement supporting nominee; (2) brief summary of nominee's achievement or contributions to retina research, plus 3 (maximum) published reprints that best substantiate the work for which he/she is being nominated; and (3) nominee's curriculum vitae including complete bibliography.

Mail completed nominations to: Alice McPherson, M.D., Retina Research Foundation, 6560 Fannin, Suite 2200, Houston, Texas 77030.

Deadline: Nominations must be postmarked no later than June 30, 1980.

Selection and Presentation: The recipient will be selected by a committee of nationally prominent vision scientists and retina specialists appointed by the Foundation. Presentation of the 1980 Award is scheduled in conjunction with the Retina Society's Annual Meeting in Philadelphia, Pennsylvania, October, 1980. The award recipient will be the named lecturer for the Charles L. Schepens Lecture, which is featured in the Retina Society Program.

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Eugene Folk, M.D. **Chicago, Ill.**	"Common Motility Consultations"
David L. Guyton, M.D. **Baltimore, Md.**	"Automated Refractions" "Topics in Motility"
Eugene Helveston, M.D. **Indianapolis, Ind.**	"Comparison of IOL's"; "Honan Pressure Reducer"
Richard P. Kratz, M.D. **Vannuys, Calif.**	"Headaches in Ophthalmology"; "The Patient with Diplopia";
Joel Sacks, M.D. **Cincinnati, O.**	"Emotional Overlay and Organic Underlay" "The 'Other' Retinal Vascular Diseases"; "Management of
Howard Schatz, M.D. **San Francisco, Calif.**	"Vitreous Hemorrhage"; "Complications of Argon Laser "Photocoagulation for Diabetic Retinopathy"

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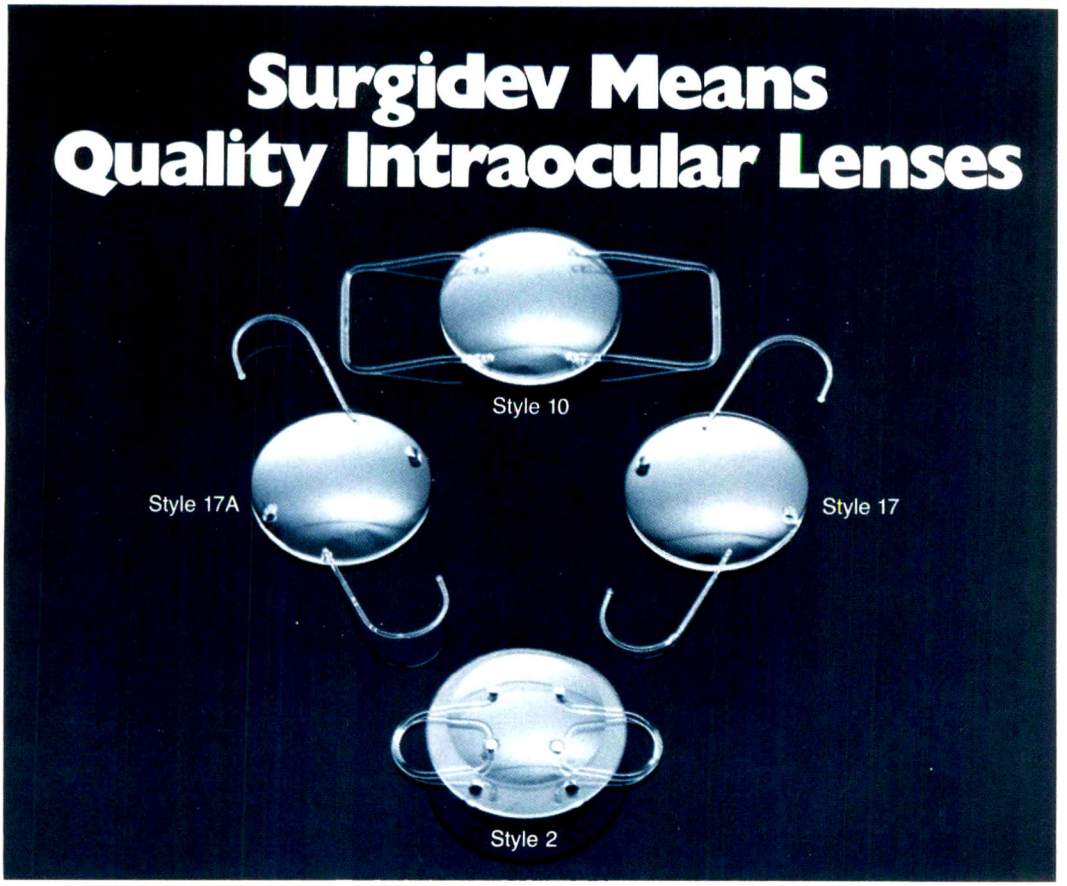

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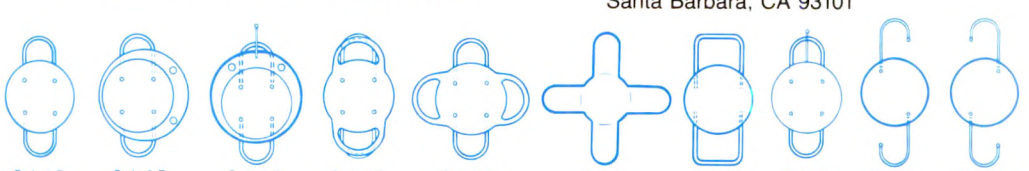

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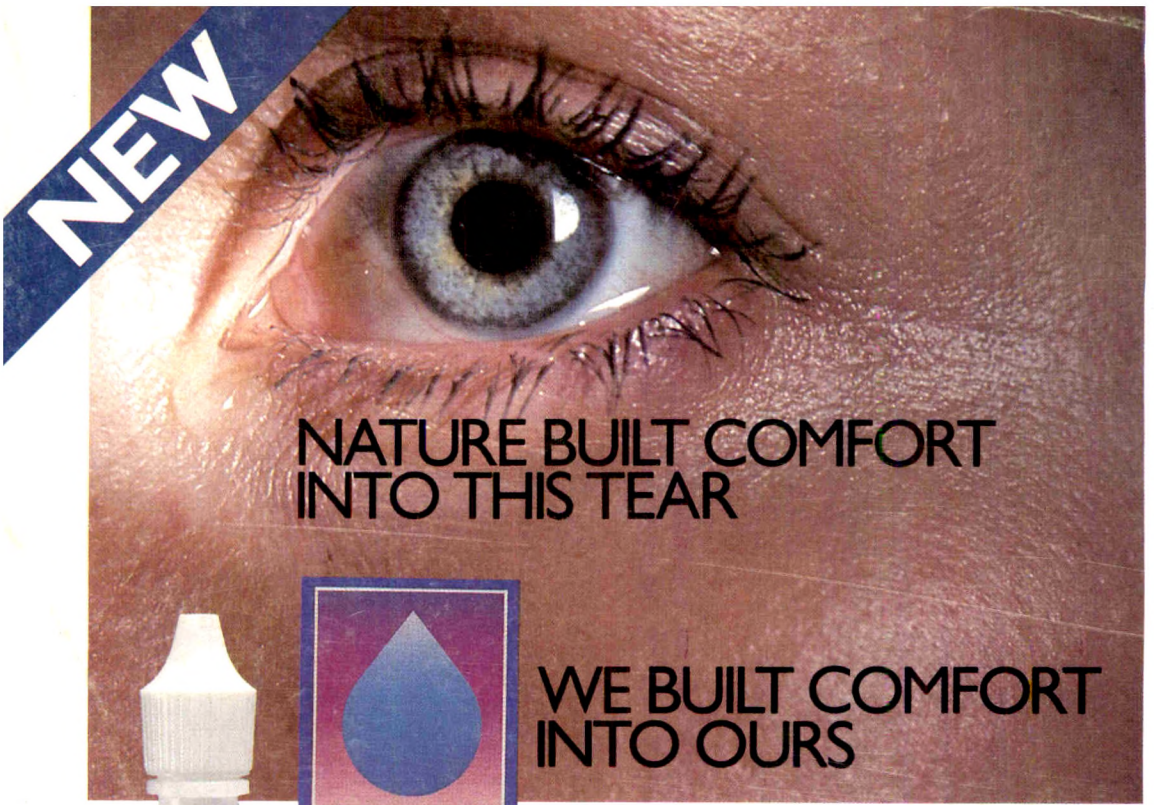

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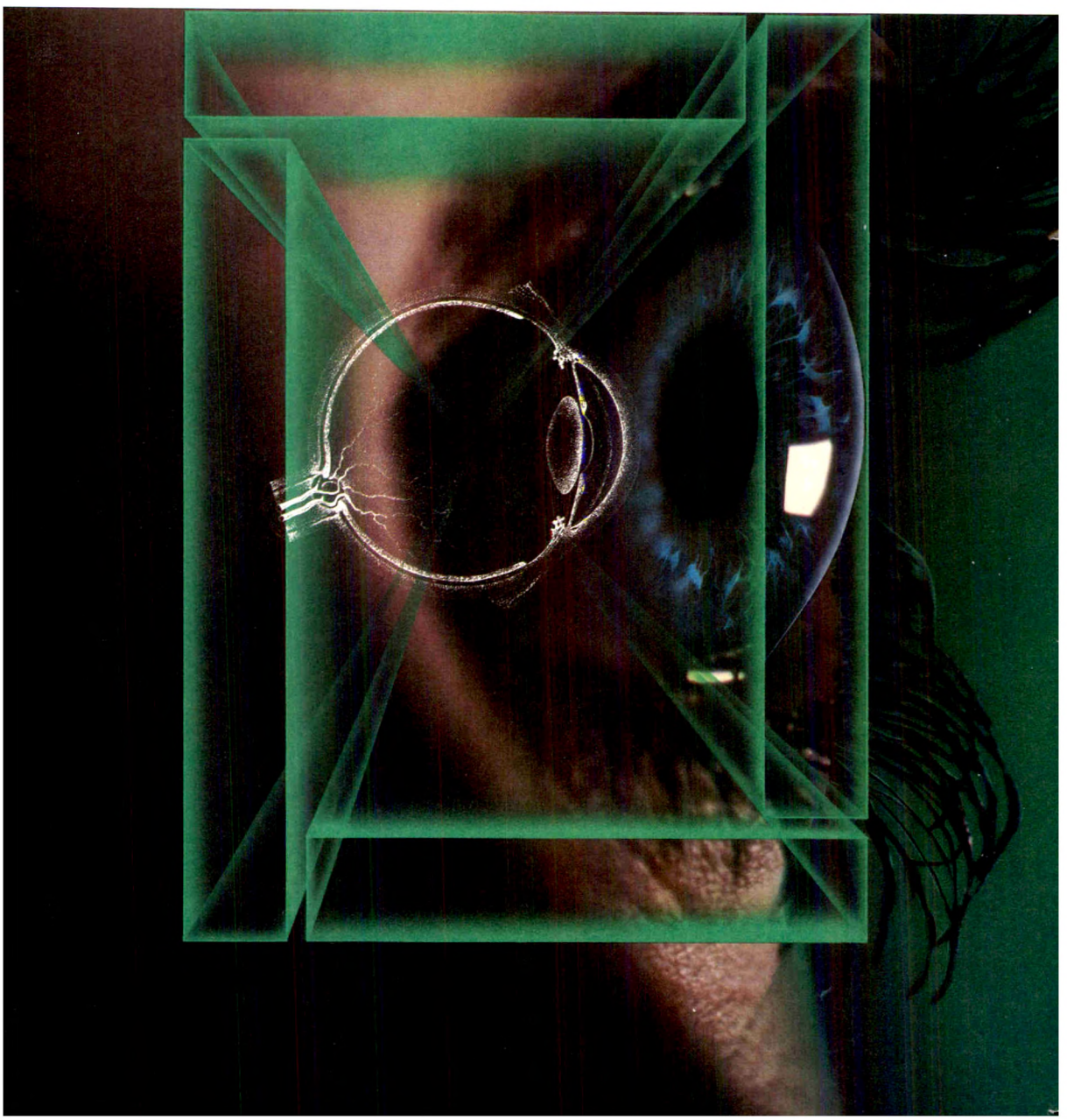

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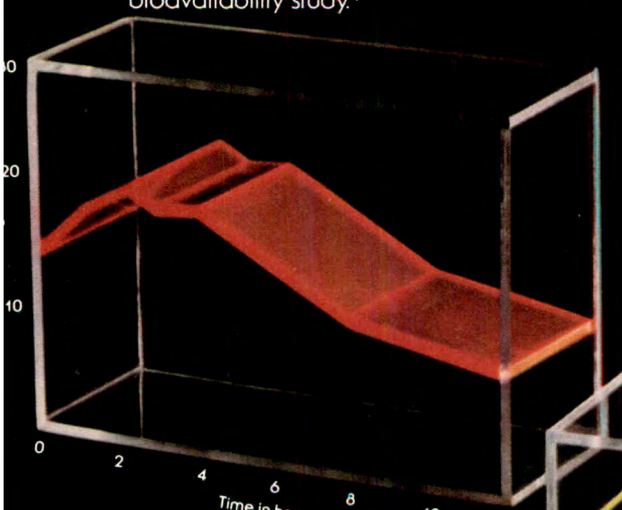

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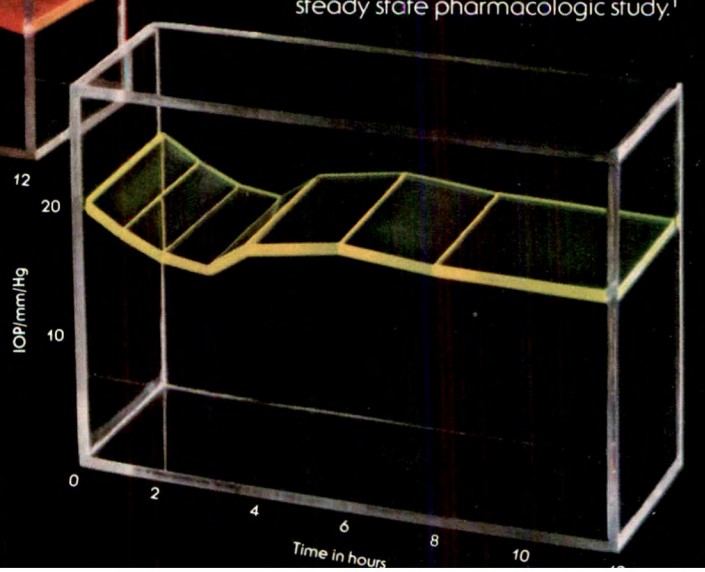

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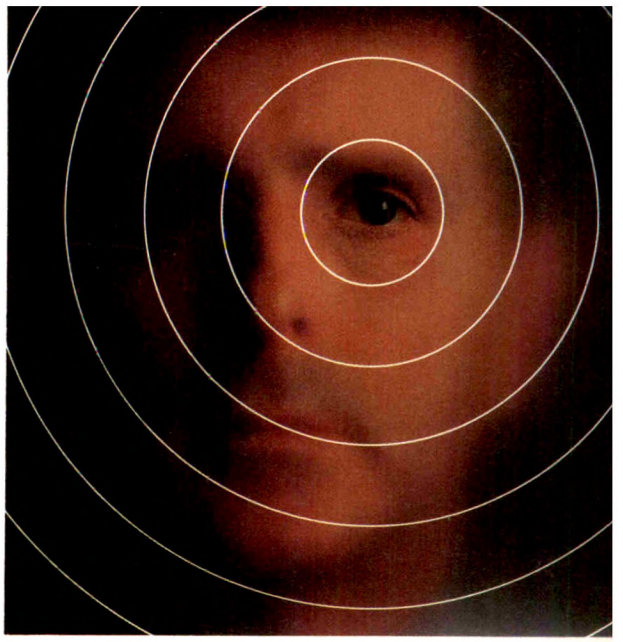

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Adverse Reactions: Prolonged use may produce extracellular pigmentation in the palpebral conjunctiva which is innocuous. On rare occasions, systemic side effects have been observed. These include occipital headaches, palpitation, paleness, acceleration of heartbeat, trembling and perspiration.

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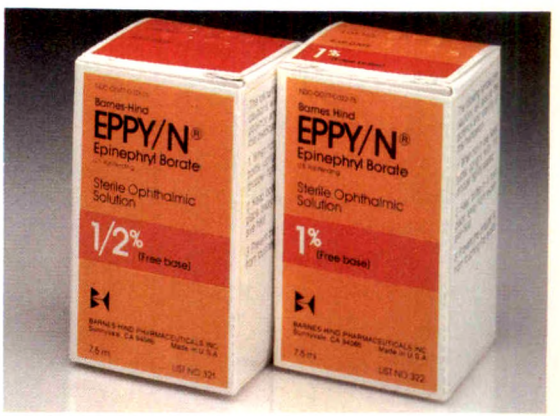

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Unger, WP: Timolol: Short Term "Escape" and Long Term "Drift" ANN OPHTH 11:8(1239) 1979.
Saunfelder, FT et al: Research Leads to More Effective Ways of Administering Eyedrops JAMA 236: 21 Nov 22 1978.

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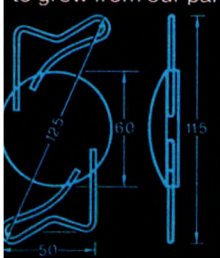

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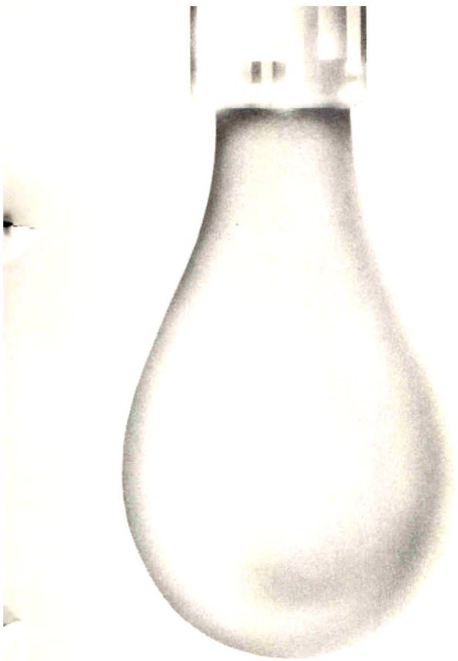

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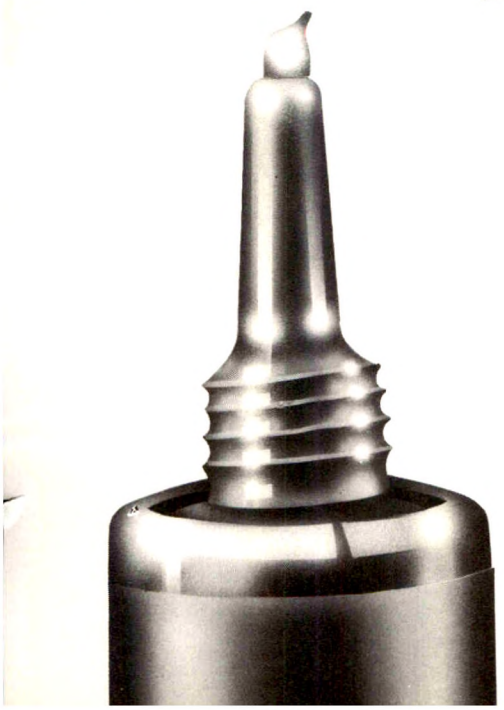

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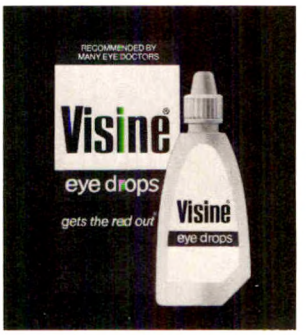

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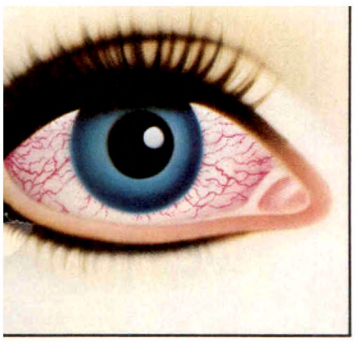

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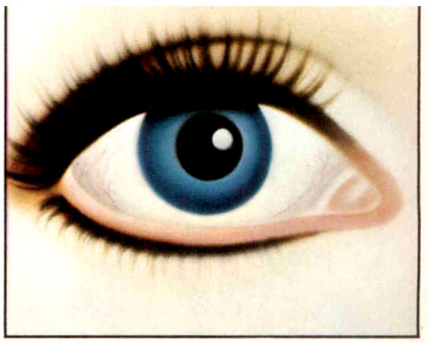

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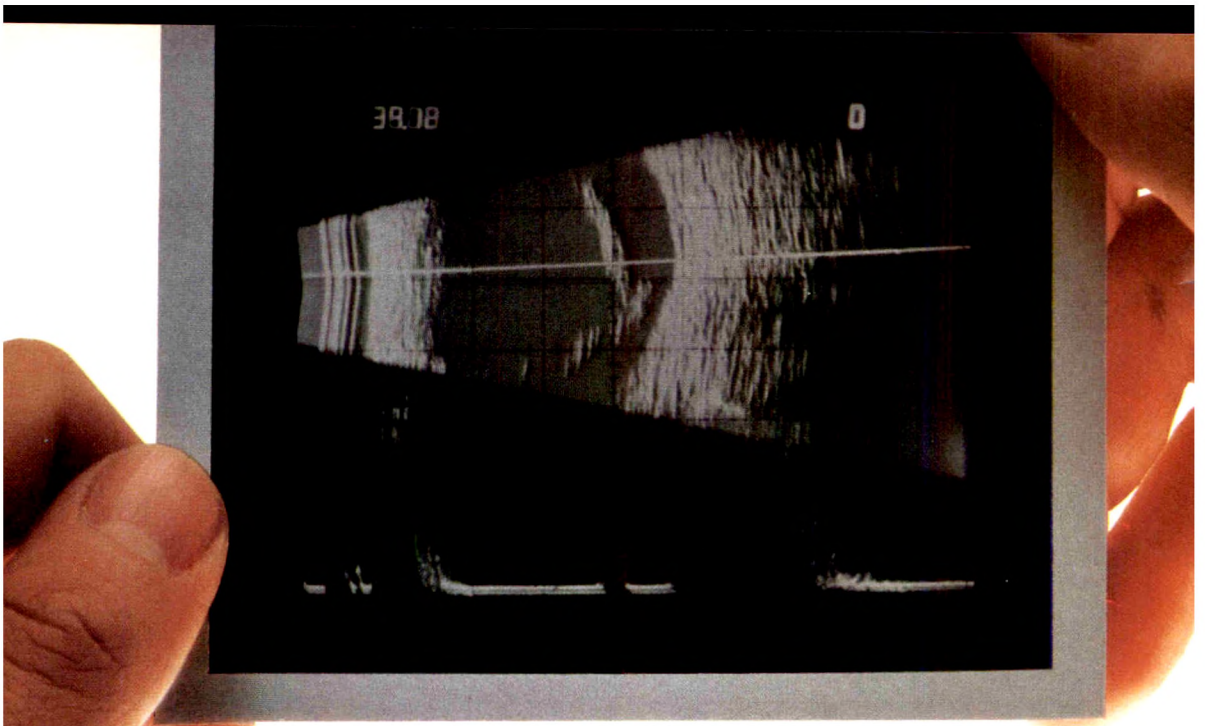

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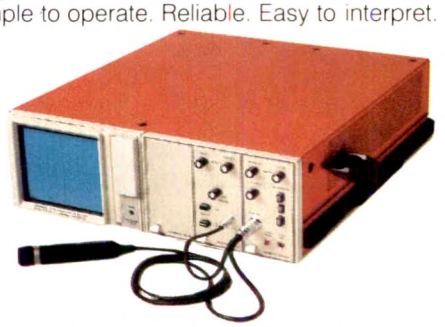

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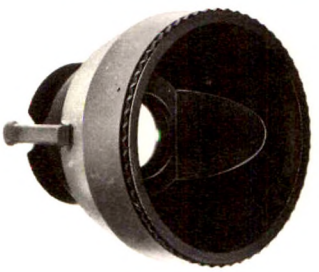

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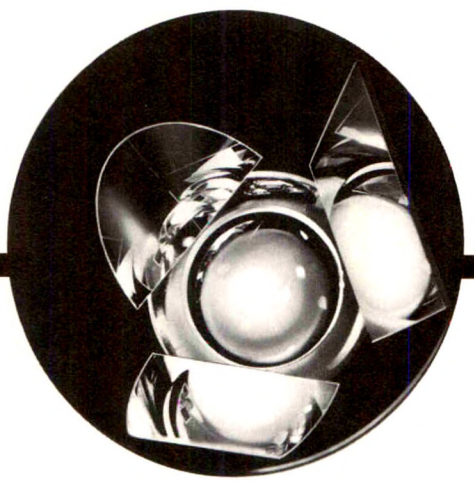

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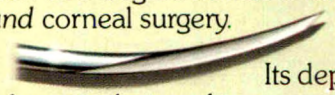

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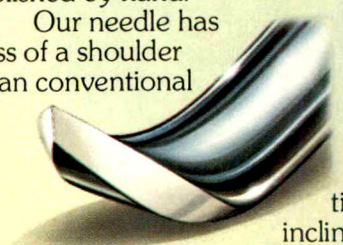

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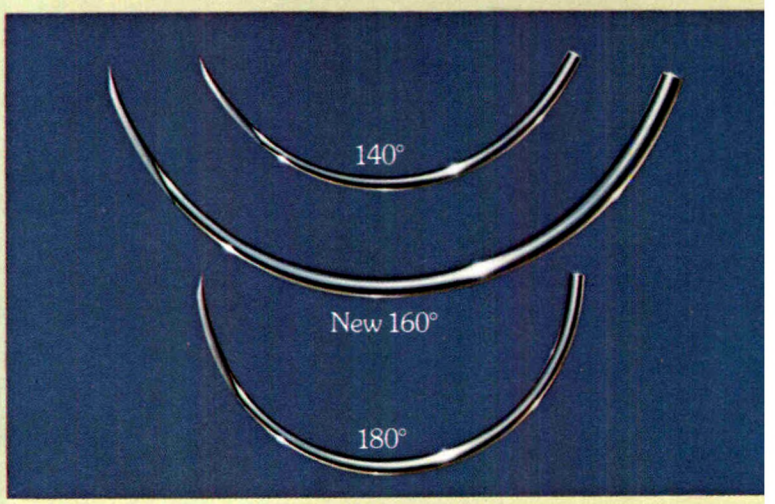

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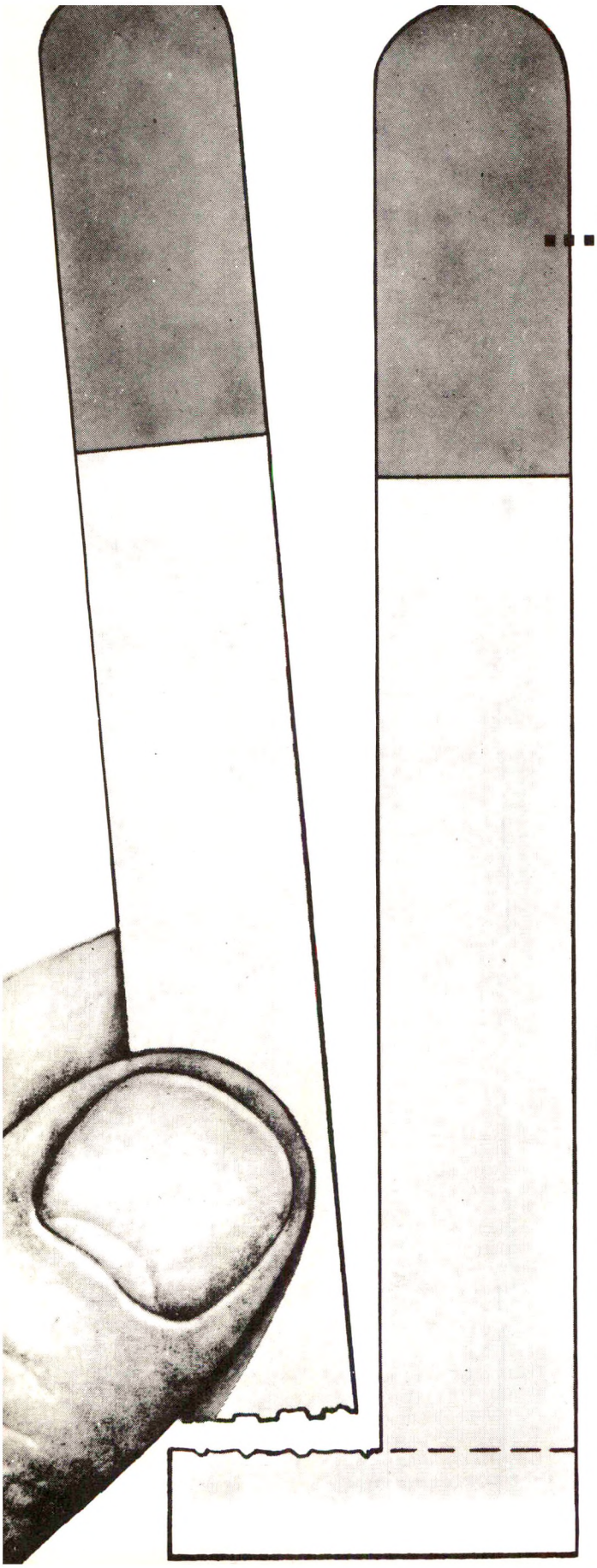

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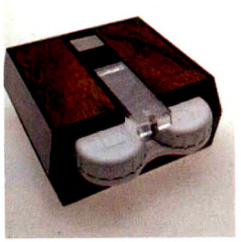
3 DISINFECT  Thermal Lens Disinfection Heating Unit	**SOFT MATE® DISINFECTION AND STORAGE SOLUTION**

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(Ptosis Surgery: Skin Approach Levator Aponeurosis Shortening)

Baikoff, G.; Colin, J.; Charleux, J. et Sourdille, Ph. (Brest): La souffrance endothéliale provoquée par un cristallin artificiel
(Endothelial Loss Caused by an Artificial Lens)

Stellpflug, H.; Busse, H.; Niedermeier, M. und Dittrich, H. (Münster): Augenveränderungen während extrakorporaler Zirkulation
(Ocular Alterations during Extracorporeal Circulation)

van der Zypen, E. and Fankhauser, F. (Bern): The Ultrastructural Features of Laser Trabeculopuncture and Cyclodialysis. Problems Related to a Successful Treatment of Chronic Simple Glaucoma

Sie, S.H. (Utrecht): Rezidiv-Prophylaxe mit Trifluorothymidin nach Keratoplastik bei Herpes corneae

Stefani, F.H. und Alexandridis, A.K. (München): Gefässveränderungen im proximalen Fasciculus opticus beim kindlichen Glaukom

Pau, H. (Düsseldorf): Metastatische Aderhauttumoren vor und nach Röntgenbestrahlung
(Metastatic Uveal Tumors Before and After Radiation)

Mester, U. (Bonn): Tierexperimentelle Ergebnisse mit Hydrogel-Keratoprothesen unterschiedlichen Wassergehaltes
(Results in Animal Experiments with Hydrogel Keratoprostheses of Different Water Content)

François, J. et Rijsselaere, M. (Gand): Kératomycoses
(Keratomycoses)

Loffredo, A.; Cennamo, G.; Sammartino, A., and Crecchio, G. de (Naples): The Value of the Association of Radiological Methods with Echographic Examination in the Study of Intraocular Foreign Bodies

Larmande, A. et Rossazza, C. (Tours): Métastases orbitaires enophtalmiantes
(Orbital Metastatic Carcinoma with Enophthalmos)

Pinckers, A.J.L. (Nijmegen): Lever's Congenital Amaurosis as Conceived by Leber

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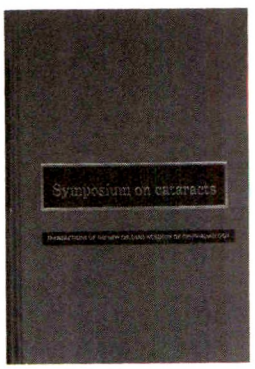

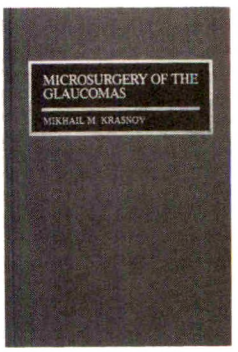

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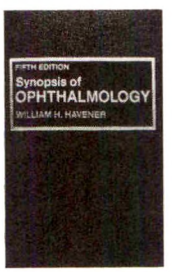

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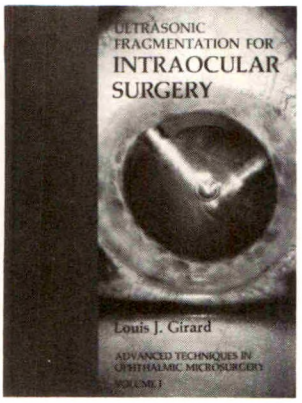

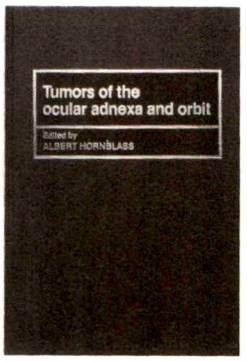

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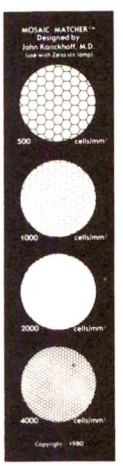

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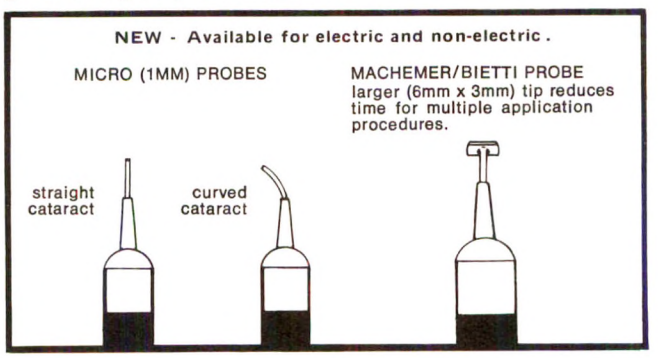

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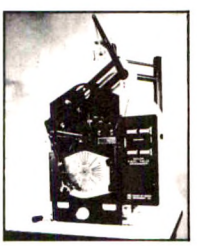

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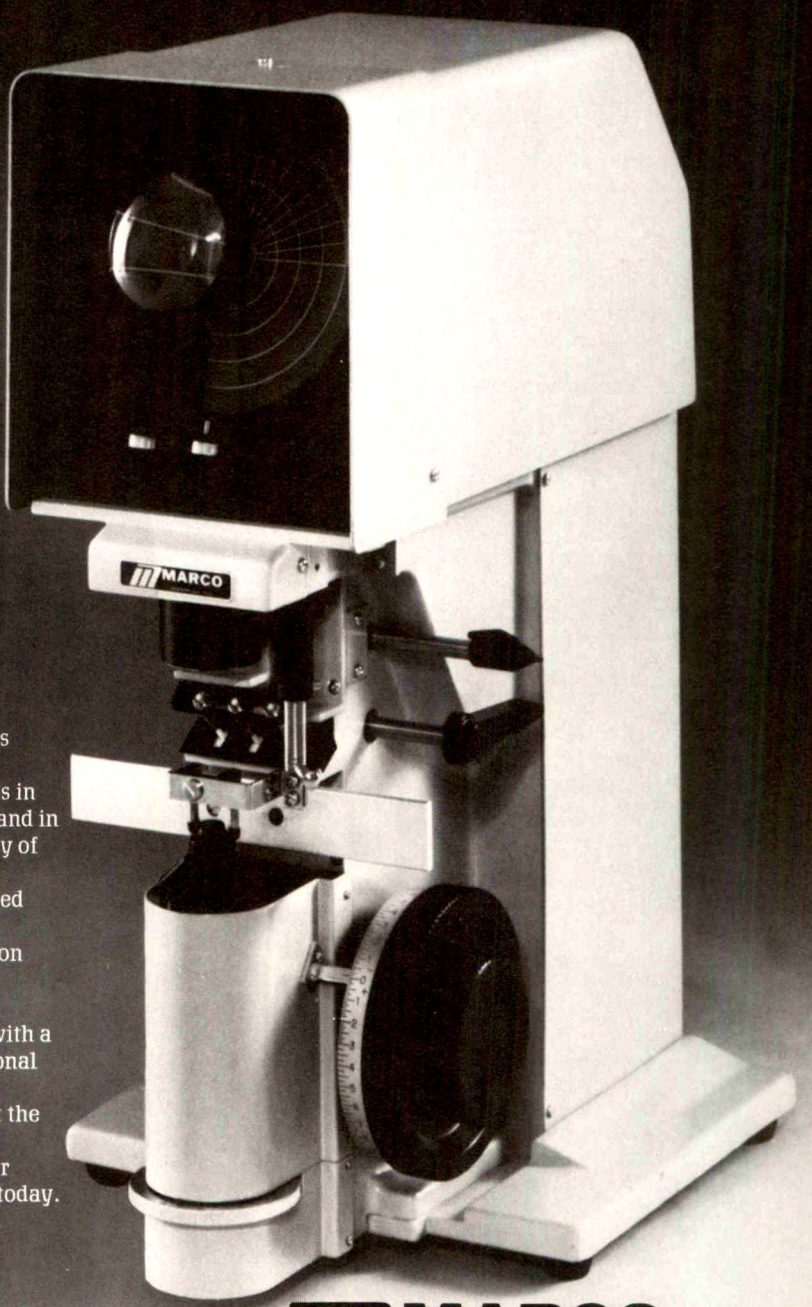

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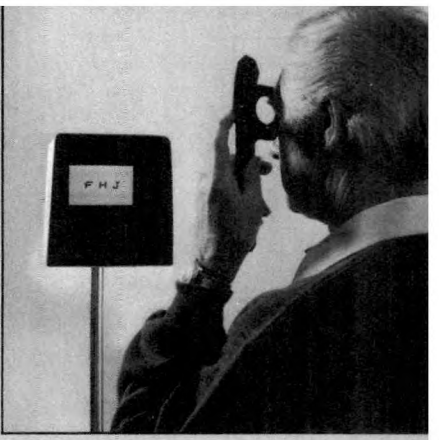

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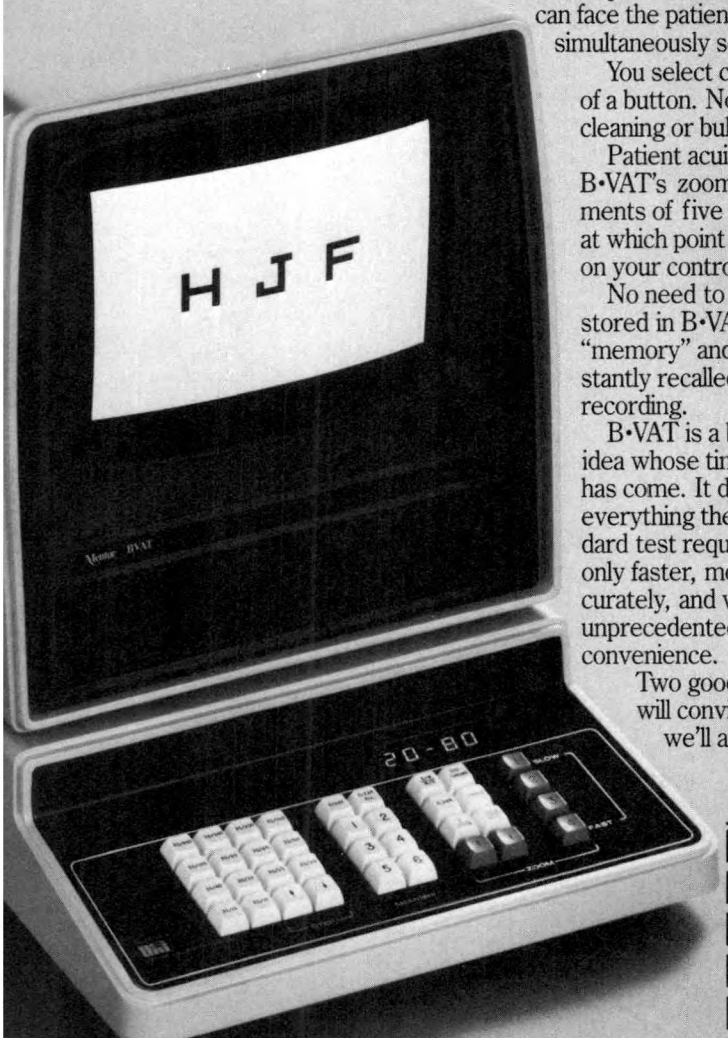

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Contemporary International Concepts

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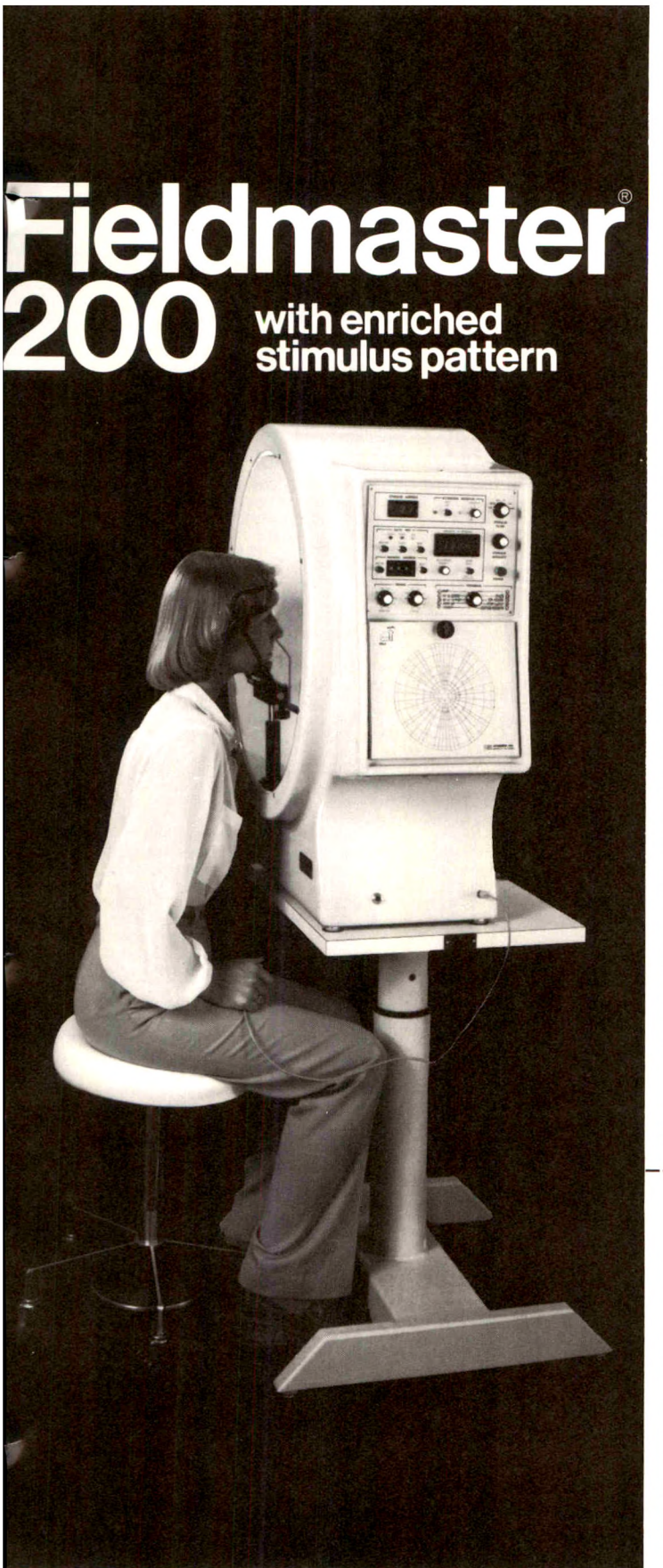

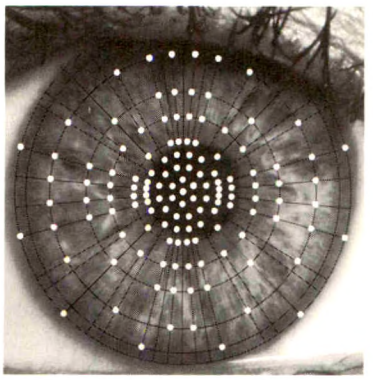

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VIRA-A®
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Description. Vira-A (vidarabine, adenine arabinoside, or Ara-A) is an antiviral drug for topical ophthalmic administration. The chemical name is 9-β-D-arabinofuranosyladenine. Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

Clinical Pharmacology. Vira-A is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Except for Rhabdovirus and Oncornavirus, Vira-A does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

The antiviral mechanism of action has not been established. Vira-A appears to interfere with the early steps of viral DNA synthesis. Vira-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of Vira-A. Because of the low solubility of Vira-A, trace amounts of both Vira-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of Vira-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, Vira-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, Vira-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit.

Indications and Usage. Vira-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. Vira-A is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions to idoxuridine have occurred. The effectiveness of Vira-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous Vira-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone, have been administered concurrently with Vira-A Ophthalmic Ointment, 3%, without an increase in adverse reactions.

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If Vira-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

Vira-A is not effective against RNA virus or adenoviral ocular infections. Vira-A is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Contraindication. Vira-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. ***Use in Pregnancy:*** Vira-A (vidarabine) parenterally is teratogenic in rats and rabbits. Ten percent Vira-A ointment applied to 10% of the body surface during organogenesis induc fetal abnormalities in rabbits. When 10% Vira-A ointment was a plied to 2 to 3% of the body surface of rabbits, no fetal abn malities were found. This dose greatly exceeds the total reco mended ophthalmic dose in humans. The possibility of embryo or fetal damage in pregnant women receiving Vira-A (vidarabi ophthalmic ointment), 3%, is remote. The topical ophthalmic do is small, and the drug relatively insoluble. Its ocular penetration very low. However, a safe dose for a human embryo or fetus h not been established. Consequently, Vira-A should be used o when clearly indicated.

It is not known whether Vira-A is excreted in human milk. A general rule, because many drugs are excreted in human m nursing should not be undertaken while a patient is under tre ment. However, excretion of vidarabine in breast milk is unlik because Vira-A is rapidly deaminated in the gastrointestinal tra

Mutagenic Potential: Results of *in vitro* experiments indica that vidarabine can be incorporated into mammalian DNA and c induce mutation in mammalian cells (mouse L5178Y cell lin Thus far, *in vivo* studies have not been as conclusive, but there some evidence (dominant lethal assay in mice) that vidarabi may be capable of producing mutagenic effects in male ge cells.

It has also been reported that vidarabine causes chromoso breaks and gaps when added to human leukocytes *in vitro*. Wh the significance of these effects in terms of mutagenicity is n fully understood, there is a well-known correlation between t ability of various agents to produce such effects and their abil to produce heritable genetic damage.

Oncogenic Potential: Chronic parenteral (IM) studies vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant crease in liver tumor incidence among the vidarabine-treat females. In the same study, some vidarabine-treated male mi developed kidney neoplasia. No renal tumors were found in t vehicle-treated control mice or the vidarabine-treated fem mice.

In the rat study, intestinal, testicular, and thyroid neoplasia c curred with greater frequency among the vidarabine-treat animals than in the vehicle-treated controls. The increases thyroid adenoma incidence in the high-dose (50 mg/kg) mal and the low-dose (30 mg/kg) females were statistically sign cant.

Hepatic megalocytosis, associated with vidarabine treatme has been found in short- and long-term rodent (rat and mou studies. It is not clear whether or not this represents a p neoplastic change.

The recommended frequency and duration of administrati should not be exceeded (see Dosage and Administration).

Precautions. The diagnosis of keratoconjunctivitis due to Herp simplex virus should be established clinically prior to prescribi Vira-A Ophthalmic Ointment, 3%.

Patients should be forewarned that Vira-A Ophthalmic Oi ment, 3%, like any ophthalmic ointment, may produce a tempor visual haze.

Although viral resistance to Vira-A has not been observed, t possibility may exist.

Adverse Reactions. Lacrimation, foreign-body sensation, c junctival injection, burning, irritation, superficial punct keratitis, pain, photophobia, punctal occlusion, and sensitiv have been reported with Vira-A Ophthalmic Ointment, 3%. T following have also been reported but appear disease-relat uveitis, stromal edema, secondary glaucoma, trophic defects, c neal vascularization, and hyphema.

Overdosage. Acute massive overdosage by oral ingestion of t ophthalmic ointment has not occurred. However, the ra deamination to arabinosylhypoxanthine should preclude a difficulty. The oral LD_{50} for vidarabine is greater than 5,020 m kg in mice and rats. No untoward effects should result from ing tion of the entire contents of a tube.

Overdosage by ocular instillation is unlikely because any e cess should be quickly expelled from the conjunctival sac. T frequent administration should be avoided.

Dosage and Administration. Administer approximately one h inch of Vira-A Ophthalmic Ointment, 3%, into the lower c junctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or compl re-epithelialization has not occurred by 21 days, other forms therapy should be considered. Some severe cases may requ longer treatment.

After re-epithelialization has occurred, treatment for an ad tional seven days at a reduced dosage (such as twice daily) recommended in order to prevent recurrence.

How Supplied. N 0071-3677-07 (Stock 18-1677-139)

Vira-A Ophthalmic Ointment, 3%, is supplied sterile ophthalmic ointment tubes of 3.5 g. The base is a 60:40 mixt of solid and liquid petrolatum.

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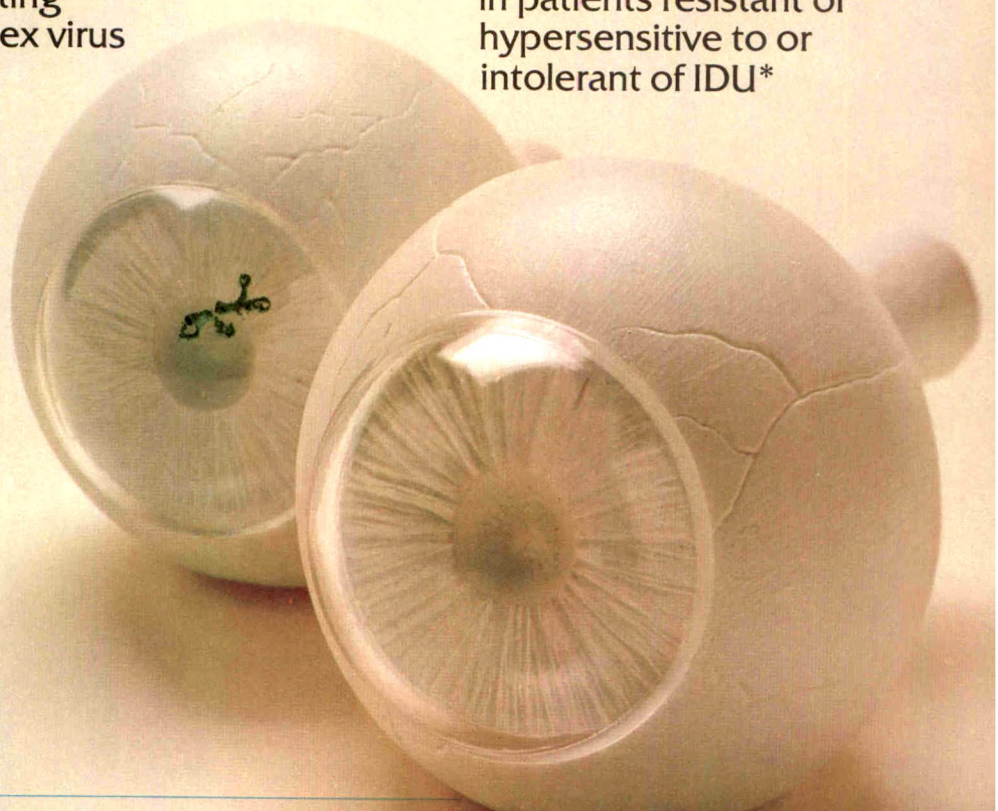

ical Evidence	No. of Subjects	Description	Effective Response
a-A ntrolled Trials	81	Previously untreated	70 subjects **(86%)**
a-A controlled Trials	142	75% had been resistant or hypersensitive to IDU	101 subjects **(71%)**

TE: In the controlled and uncontrolled trials, 70 and 101 subjects, pectively, re-epithelialized at the end of three weeks on Vira-A.

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Vira-A is preservative-free.

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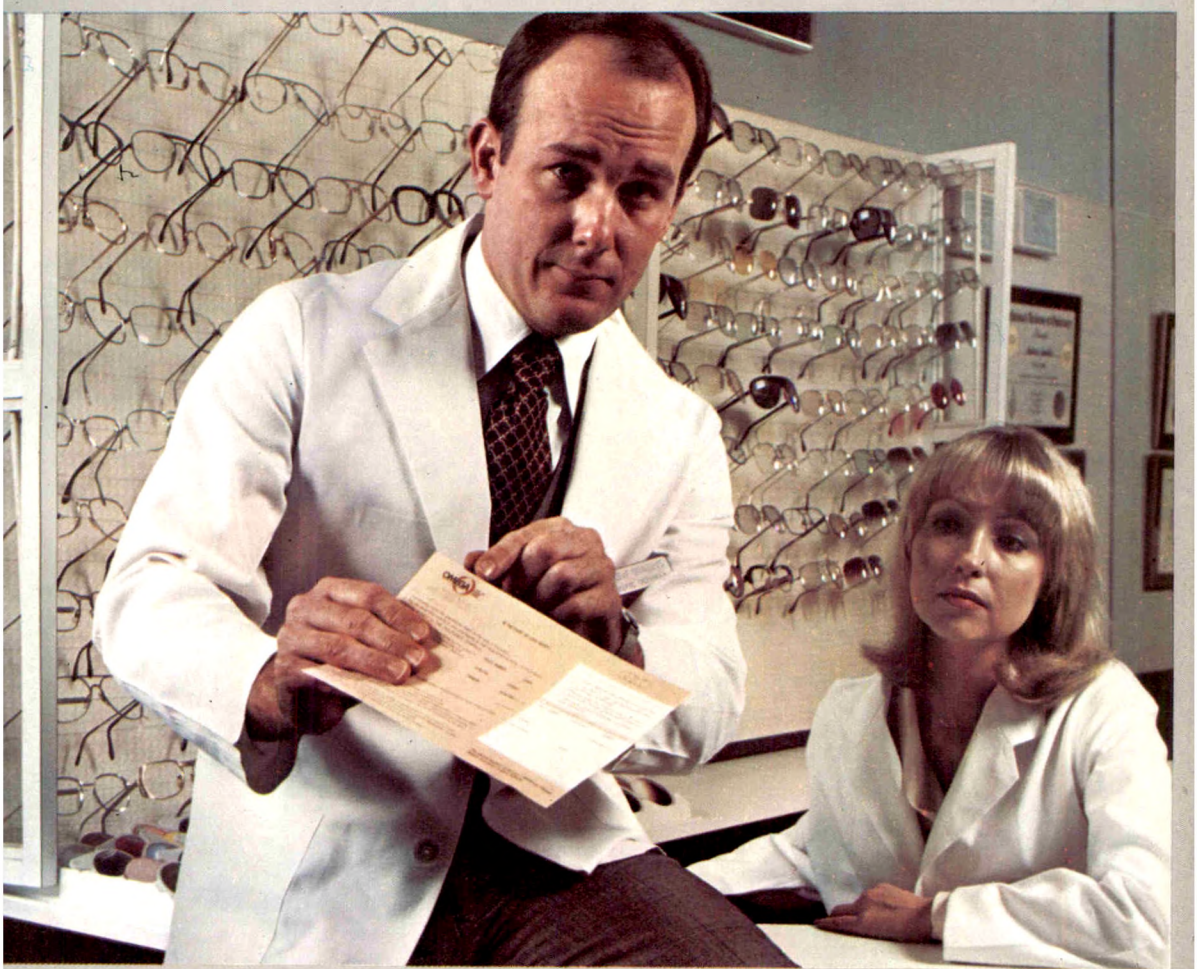

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Solution-Sterile
Ointment-Sterile

Each ml. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

- **Broad-spectrum activity against many gram-negative and gram-positive oculopathogens (see prescribing information below) frequently implicated in commonly seen infections of the external eye and its adnexa.**
- **Single-entity antibiotic.**
- **Generally low potential for sensitivity reactions and irritation.**

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci; and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species, including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube, boxes of one and six. Store away from heat.

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NOVEMBER 1973

For complete details, consult package insert or literature available from your Schering Representative; or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

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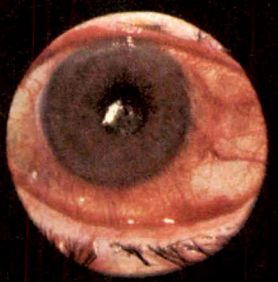
SWW-4120

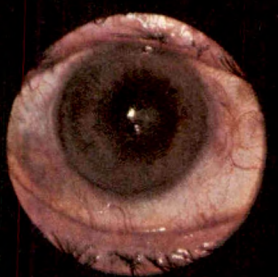
cute catarrhal conjunctivitis
episcleritis. Etiology: S. aureus.
Before treatment.

th day post treatment with
GARAMYCIN Ophthalmic.
Culture negative.

Corneal ulcer.
Etiology: S. aureus.
Before treatment.



17th day post treatment with
GARAMYCIN Ophthalmic.
Culture negative.



Acute hemorrhagic conjunctivitis.
Etiology: Pneumococcus.
Before treatment.

4th day post treatment with
GARAMYCIN Ophthalmic.
Culture negative.

Corneal marginal ulcer.
Etiology: S. aureus.
Before treatment.

10th day post treatment with
GARAMYCIN Ophthalmic.
Culture negative.

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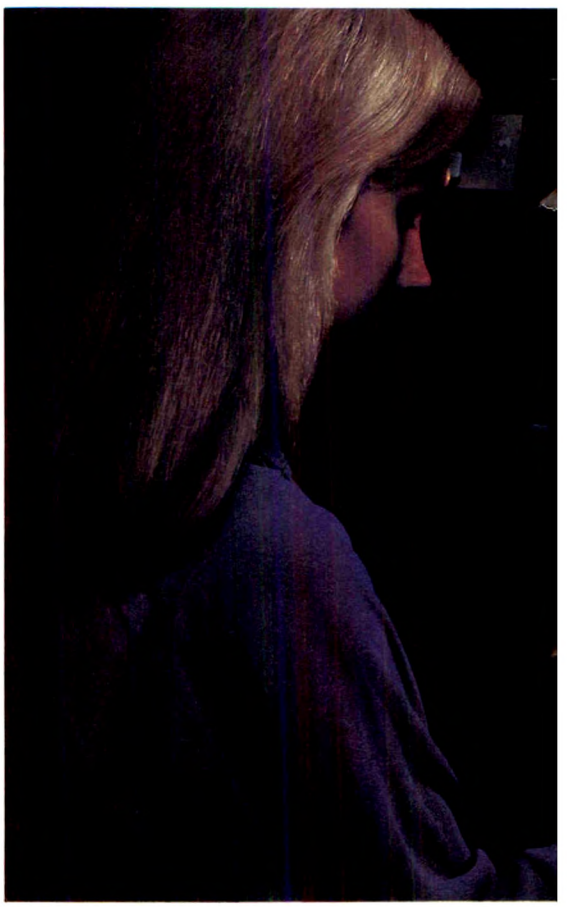

Until now you had little choice.
You could perform all the refractions yourself from start to finish, or buy a staff-operated auto-refractor to provide a starting point for the rest of the examination. In either case, there was no way to actually reduce the number of refractions you personally performed.
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Suppose your practice consists of a large number of "no-change" patients – those who do not need, and do not expect, new glasses. Studies show this group may comprise between 25-45% of your practice. The SR III identifies these patients and makes a refraction by you unnecessary. Since the instrument provides V.A. for both aided and unaided vision, you have the data to confidently state that a new Rx would not significantly improve the patient's vision. Or suppose your practice consists of a high number of IOL, cataract, or contact lens patients. The SR III excels with these repetitive and time-consuming follow-ups and provides exactly what you need – a status report.
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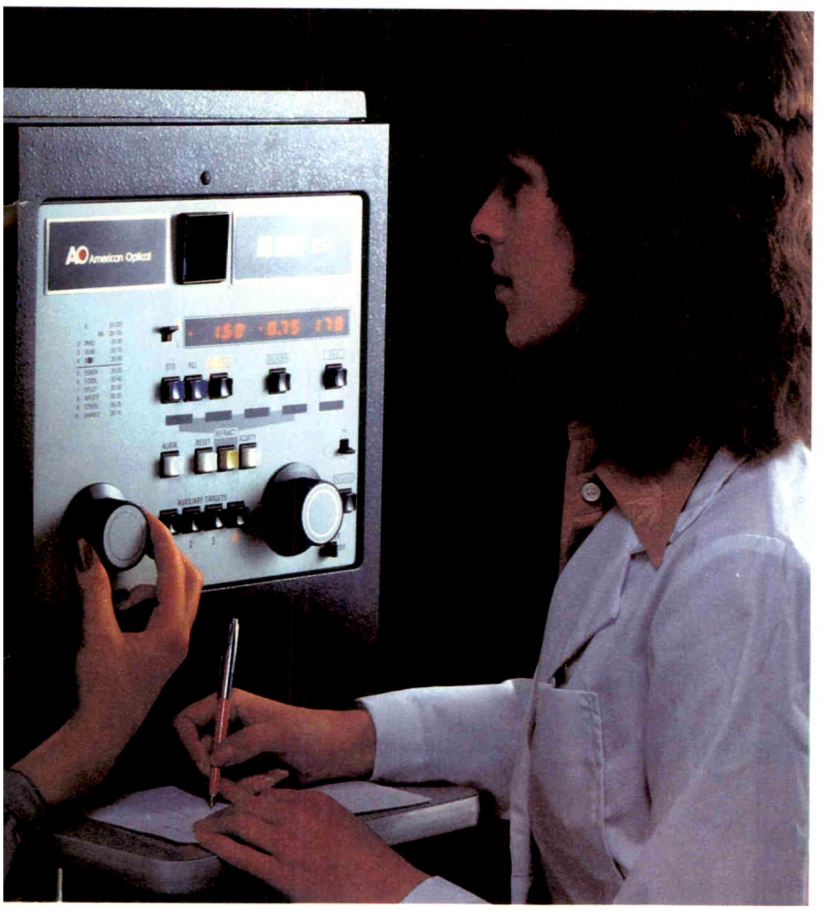

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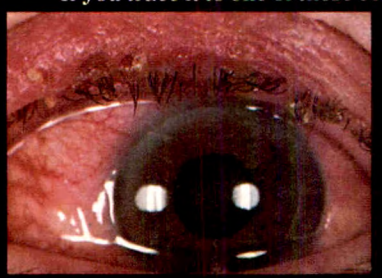


*Acute bacterial conjunctivitis**
Marked by itching or burning, hyperemia, lid edema and lacrimation or purulent discharge. Second only to refractive errors in frequency among ocular complaints.

*Bacterial corneal ulcer**
Pain, photophobia, lacrimation and blepharospasm are usual presenting symptoms. Prompt institution of therapy is vital to avoid possible visual difficulty.

*When due to susceptible microorganisms.

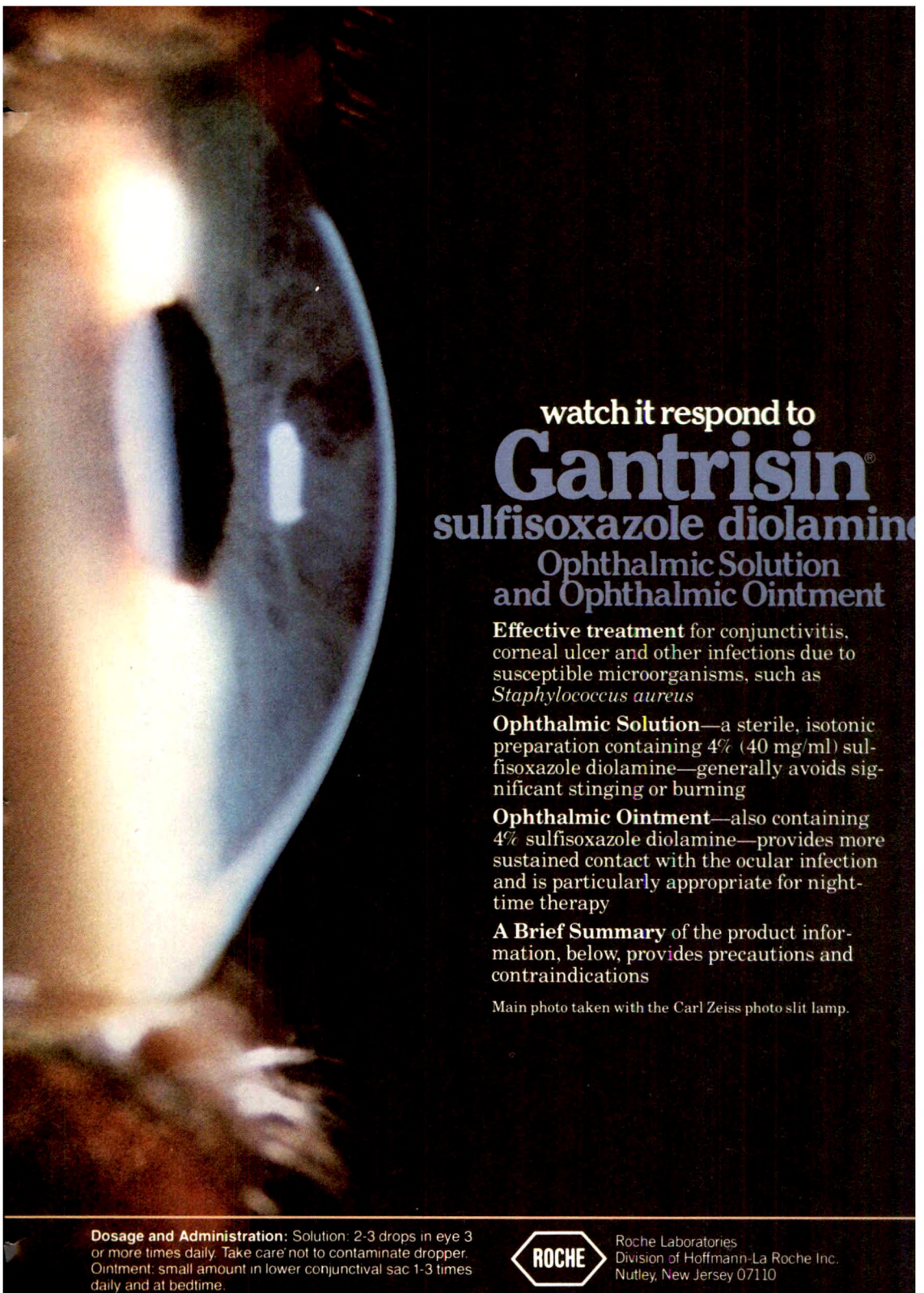
Gantrisin® **sulfisoxazole diolamine/Roche**
Ophthalmic Solution, Ophthalmic Ointment

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Conjunctivitis, corneal ulcer, other superficial ocular infections due to susceptible microorganisms; as adjunct in systemic sulfonamide therapy of trachoma.

Contraindications: Hypersensitivity.

Precautions: Incompatible with silver preparations; inactivated by para-aminobenzoic acid in purulent exudates; may increase growth of nonsusceptible organisms, including fungi. Ointment may retard corneal healing. Discontinue use



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Ophthalmic Solution and Ophthalmic Ointment

Effective treatment for conjunctivitis, corneal ulcer and other infections due to susceptible microorganisms, such as *Staphylococcus aureus*

Ophthalmic Solution—a sterile, isotonic preparation containing 4% (40 mg/ml) sulfisoxazole diolamine—generally avoids significant stinging or burning

Ophthalmic Ointment—also containing 4% sulfisoxazole diolamine—provides more sustained contact with the ocular infection and is particularly appropriate for nighttime therapy

A Brief Summary of the product information, below, provides precautions and contraindications

Main photo taken with the Carl Zeiss photo slit lamp.

Dosage and Administration: Solution: 2-3 drops in eye 3 or more times daily. Take care not to contaminate dropper. Ointment: small amount in lower conjunctival sac 1-3 times daily and at bedtime.

How Supplied:

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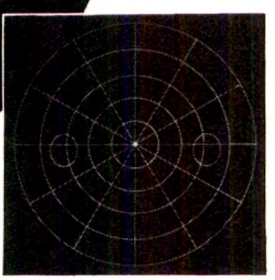

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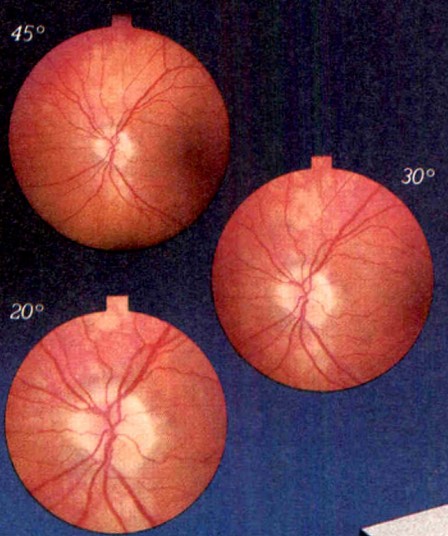

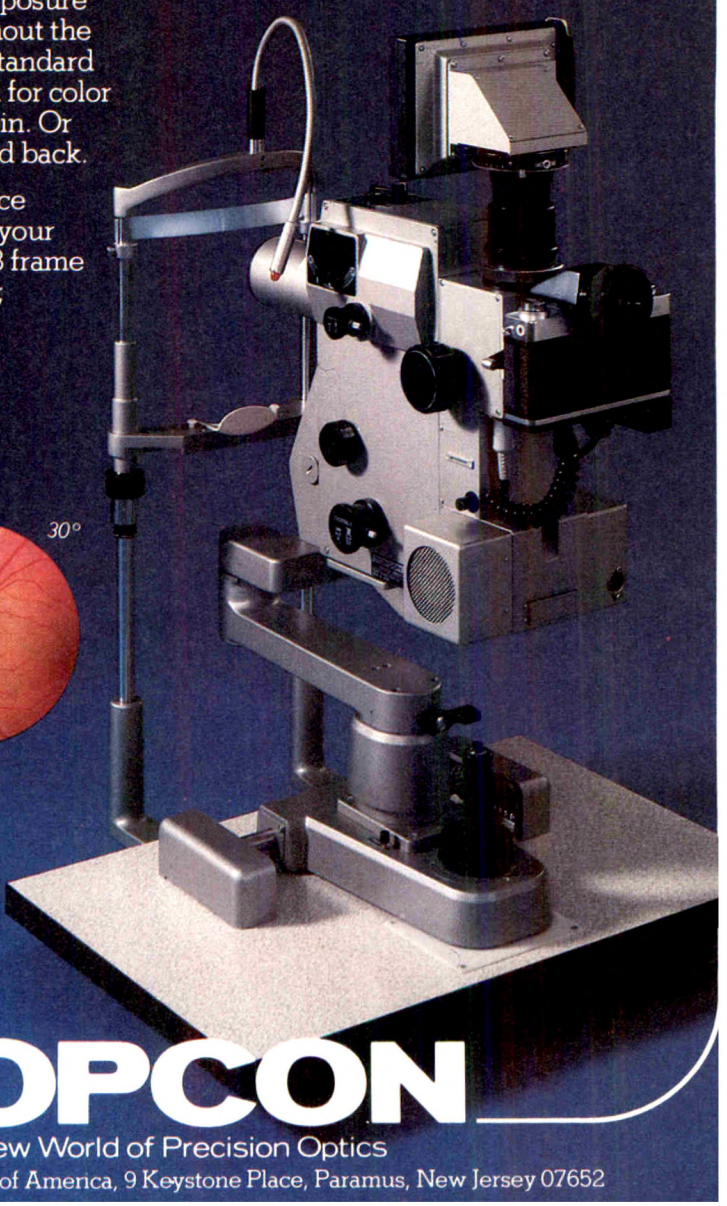

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under the direction of
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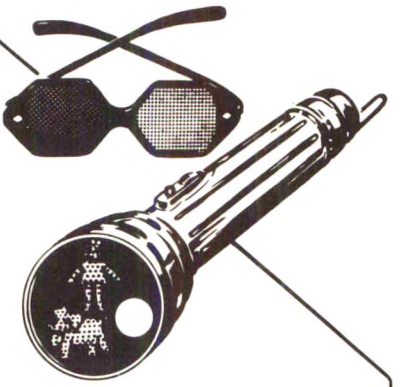

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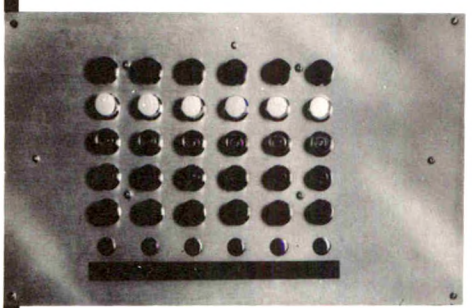

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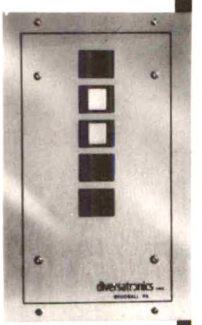

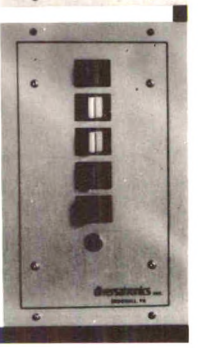

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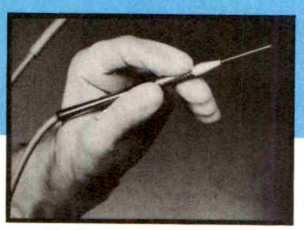
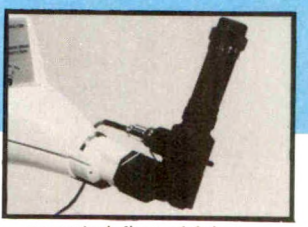


Charles endophotocoagulator

Iris coagulator attachment



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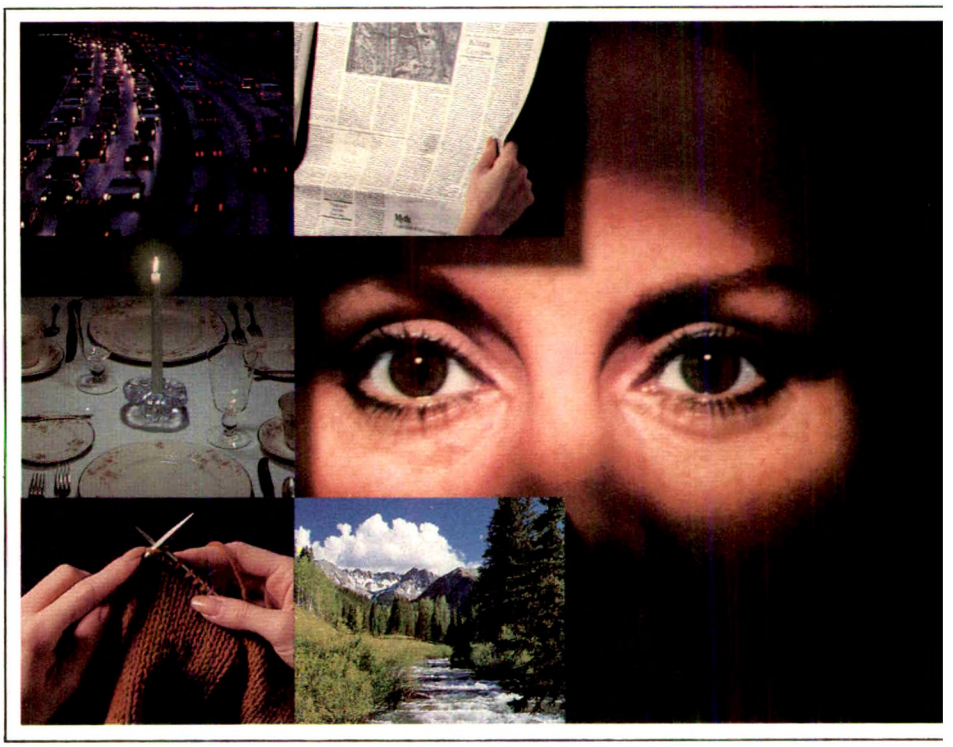
In chronic open-angle glaucoma therapy

Two good reasons to switch patients to



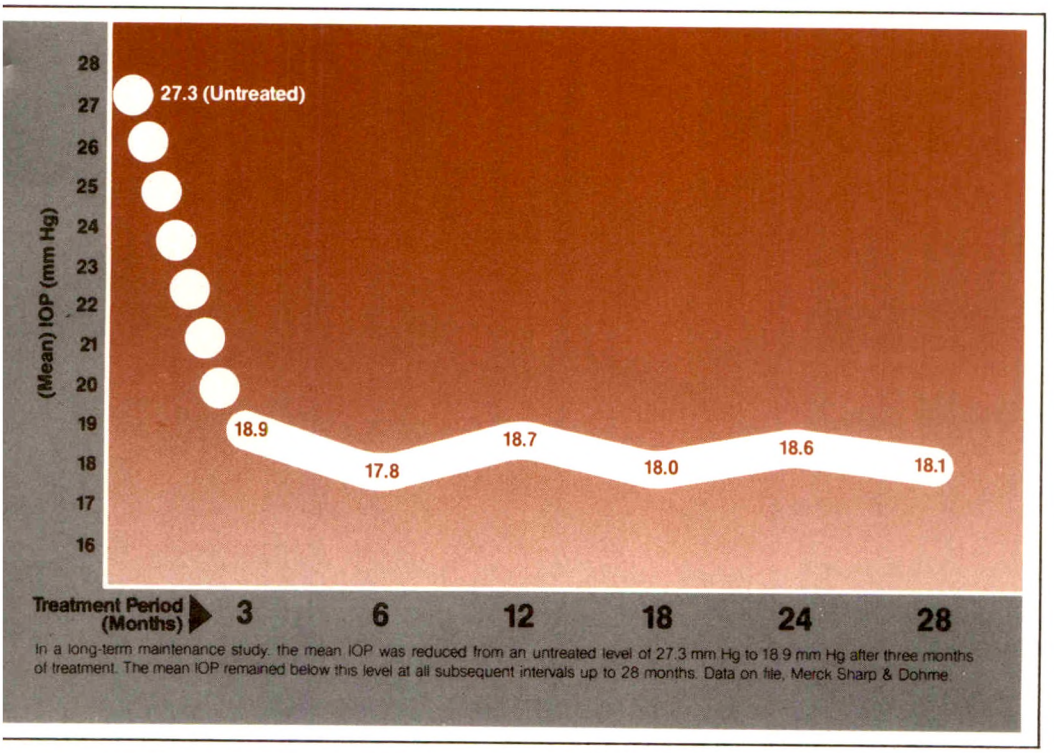
1. A better quality of life for many patients...

Patients on TIMOPTIC® (Timolol Maleate, MSD) generally do *not* experience the following therapy-limiting side effects:

change in pupil size/dimming of vision/night blindness*

TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product. Occasionally, mild ocular irritation has been reported.

Timoptic®
(TIMOLOL MALEATE | MSD)
OPHTHALMIC SOLUTION



In a long-term maintenance study, the mean IOP was reduced from an untreated level of 27.3 mm Hg to 18.9 mm Hg after three months of treatment. The mean IOP remained below this level at all subsequent intervals up to 28 months. Data on file, Merck Sharp & Dohme

2. Efficacy maintained in long-term therapy...

- No tolerance was observed in 102 patients for 28 months
- TIMOPTIC was significantly more effective than pilocarpine or epinephrine in reducing elevated IOP*
- TIMOPTIC reduced IOP in 3 out of 4 patients*

*Based on controlled multiclinic studies, evaluating over 1000 patients.

MSD
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For a brief summary of Prescribing Information, please see following page. Copyright © 1979 by Merck & Co., Inc.

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a beta-adrenergic blocking agent in ophthalmic solution

a significant advance for the reduction of IOP in:

- chronic open-angle glaucoma
- aphakic glaucoma
- some patients with secondary glaucoma
- ocular hypertension
- some patients who respond inadequately to multiple antiglaucoma drug therapy

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in each eye twice a day.

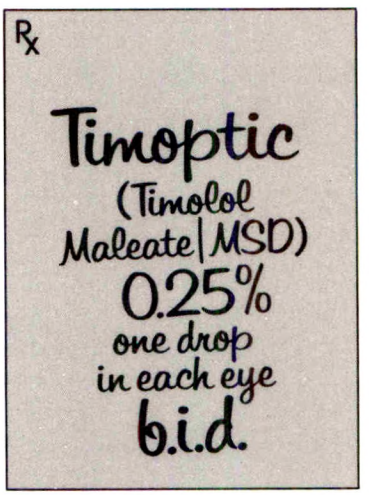
How to transfer from current therapy to TIMOPTIC:
1. On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC in each eye b.i.d.

2. On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC in each eye b.i.d.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in each eye. Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in each eye.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.



CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.
PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.
Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.
Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.
ADVERSE REACTIONS: Occasionally, signs and symptoms of mild ocular irritation have been reported. Local hypersensitivity reactions, including localized and generalized rash, have occurred rarely.

Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Rarely, episodes of acute bronchospasm have been reported in patients with bronchospastic disease (see PRECAUTIONS).
Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studied in patients wearing lenses made with materials other than PMMA.
HOW SUPPLIED:
TIMOPTIC Ophthalmic Solution, 0.25%
TIMOPTIC Ophthalmic Solution, 0.5%
Both are available in 5-ml and 10-ml plastic OCUMETER® Ophthalmic Dispensers with a controlled drop tip.
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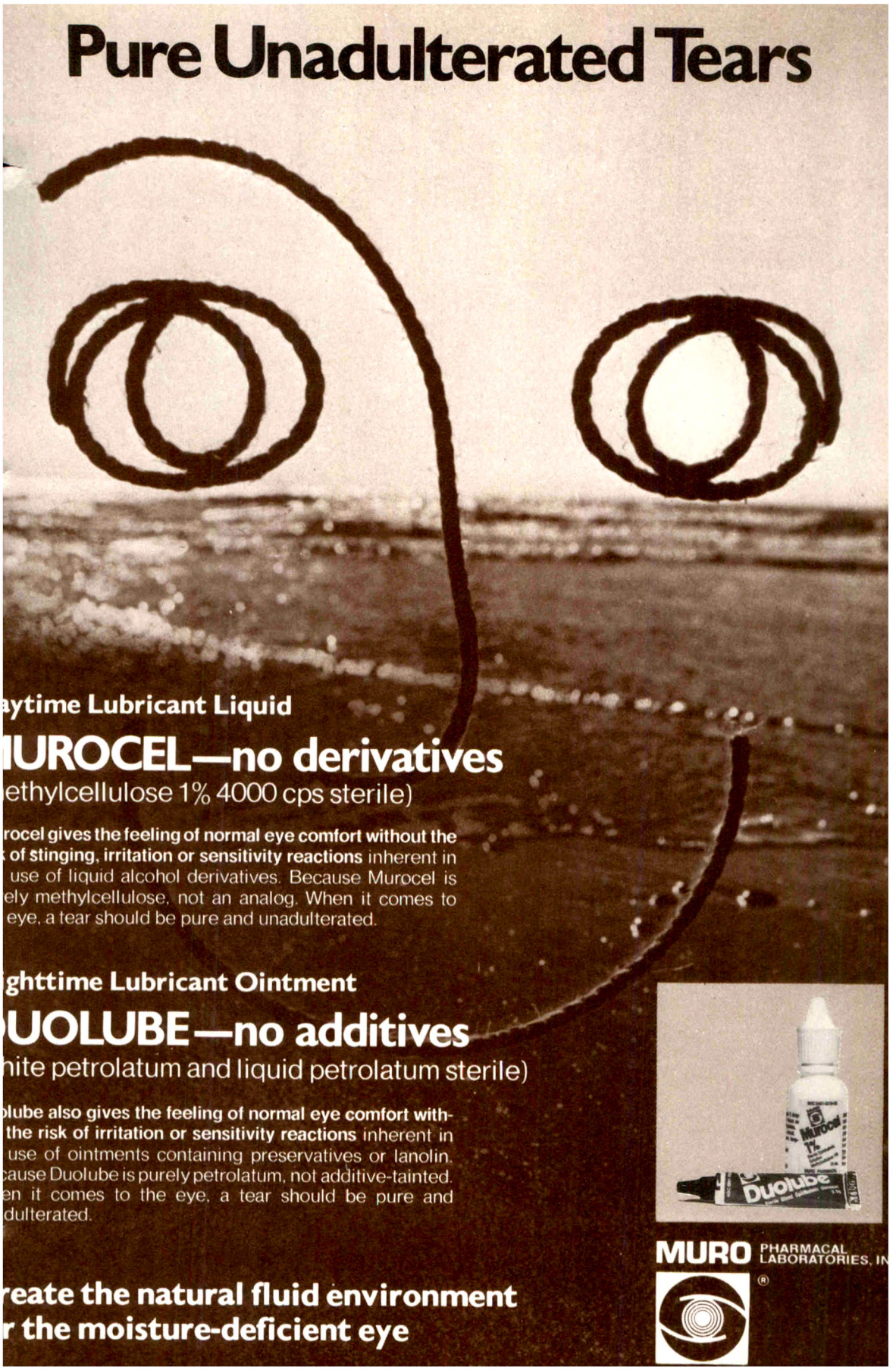

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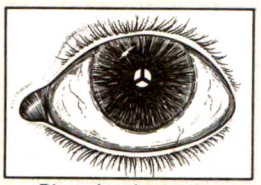
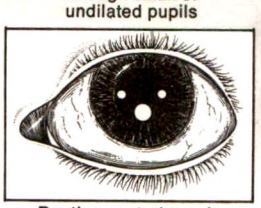
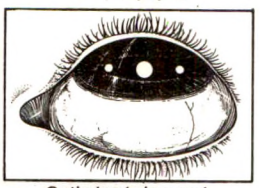


Binocular observation through small or undilated pupils



Routine posterior pole observation through dilated pupils



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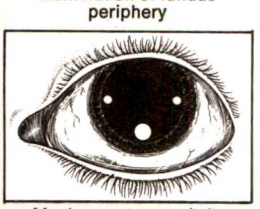

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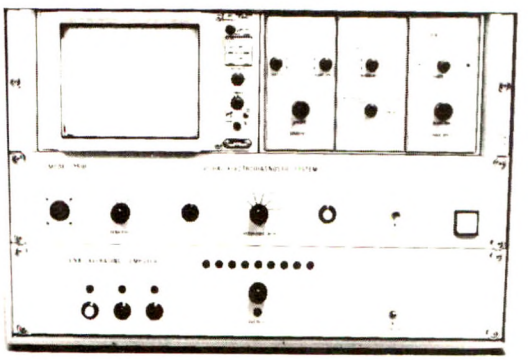

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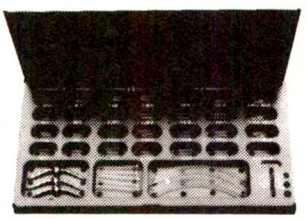

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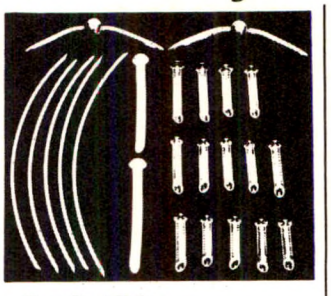

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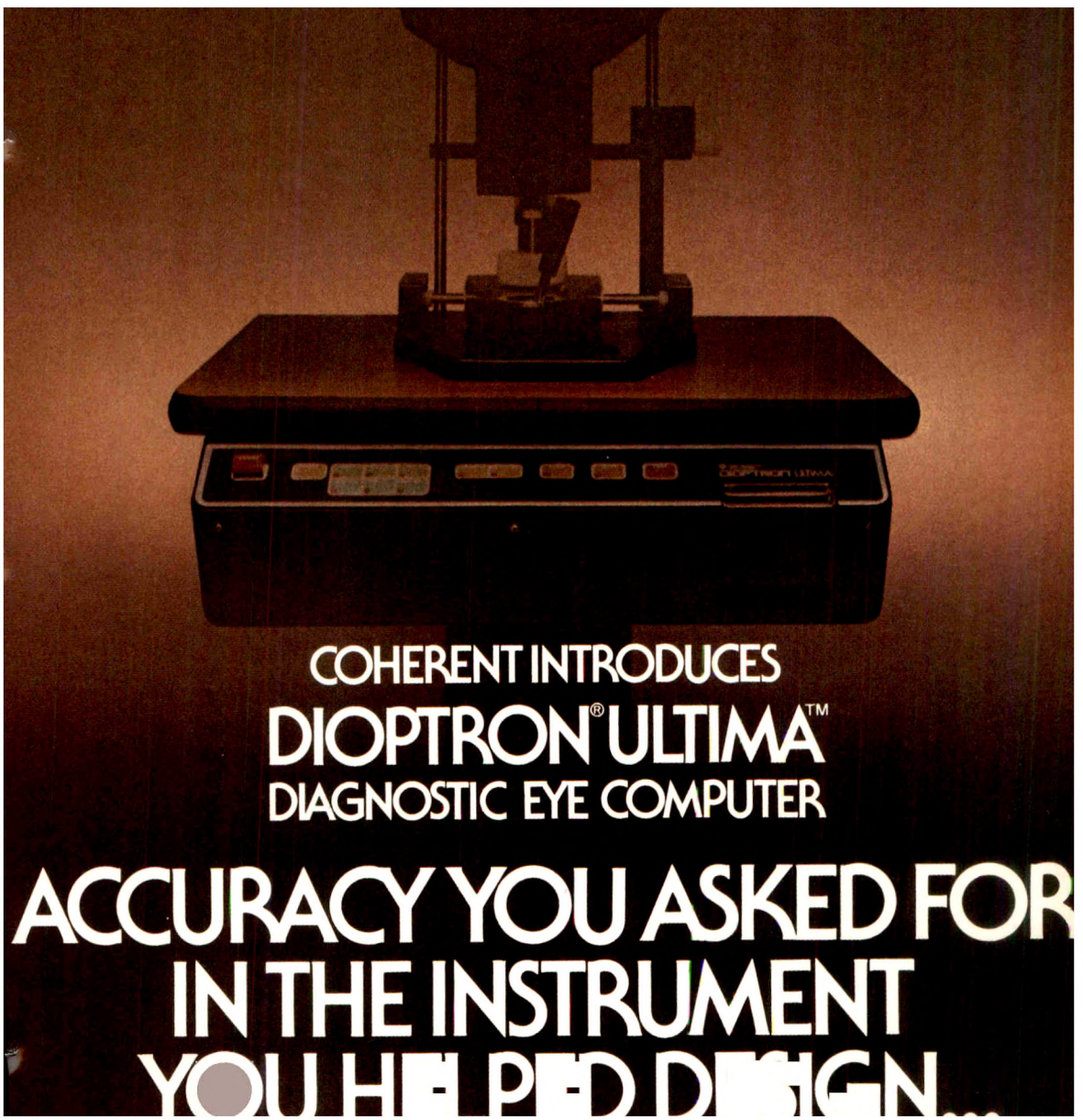
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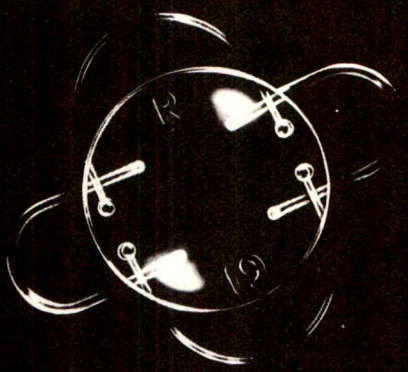

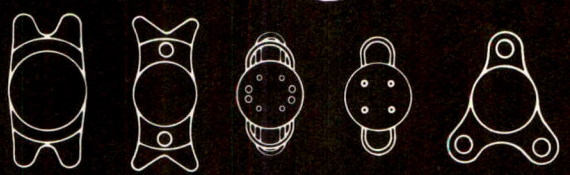

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THE SOUTHERN CALIFORNIA LIONS EYE INSTITUTE
at
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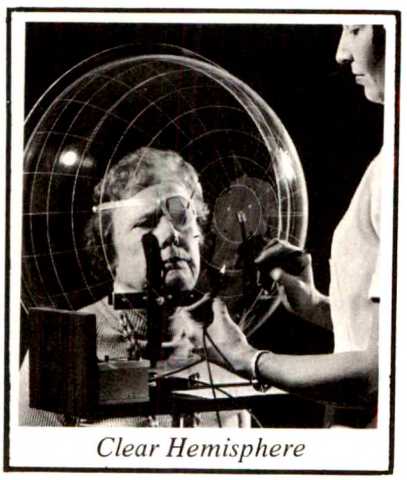

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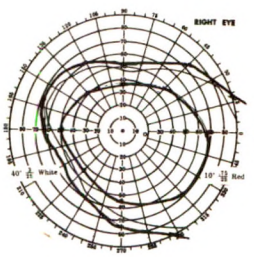
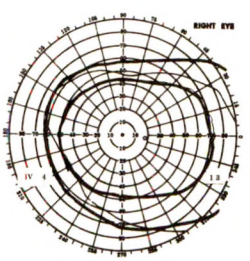
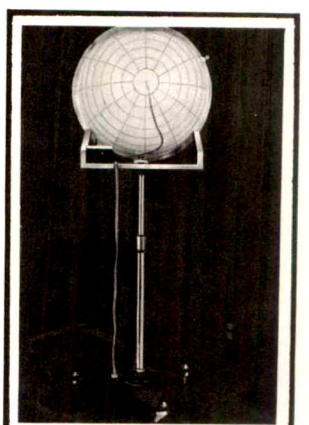


Goldman Perimeter
38 yr. old healthy woman



#921 Universal Perimeter, complete with fiber optics, caps for reducing the target size, Red and Black grease pencils, pad of special charts, and stand with casters (specify clear or frosted hemisphere)

#920 Universal Perimeter, without stand for table mounting.



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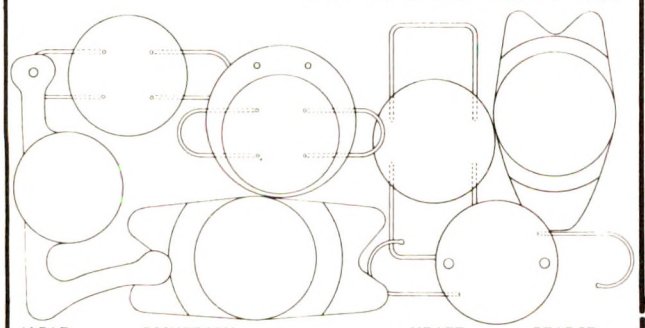
BY DENNIS D. SHEPARD, M.D. FACS



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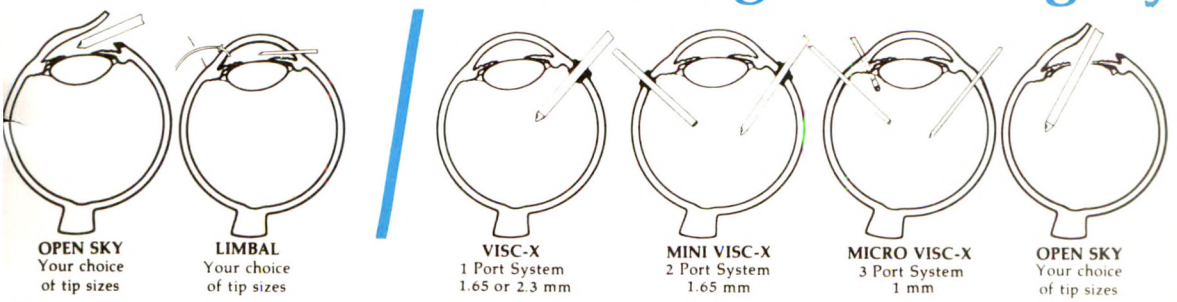
Anterior or Posterior Segment Surgery



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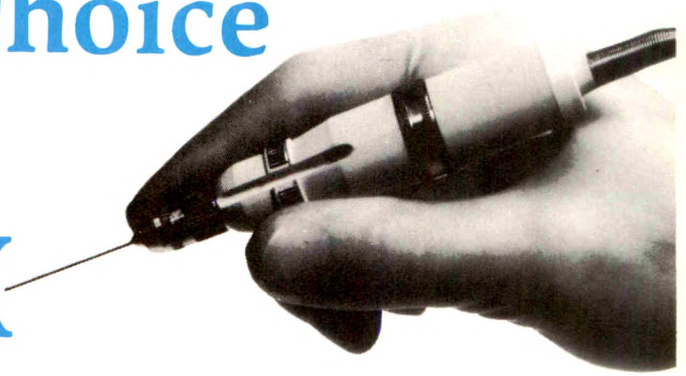

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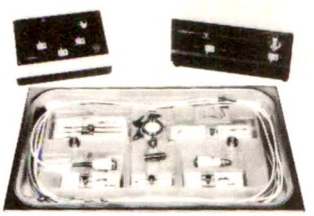

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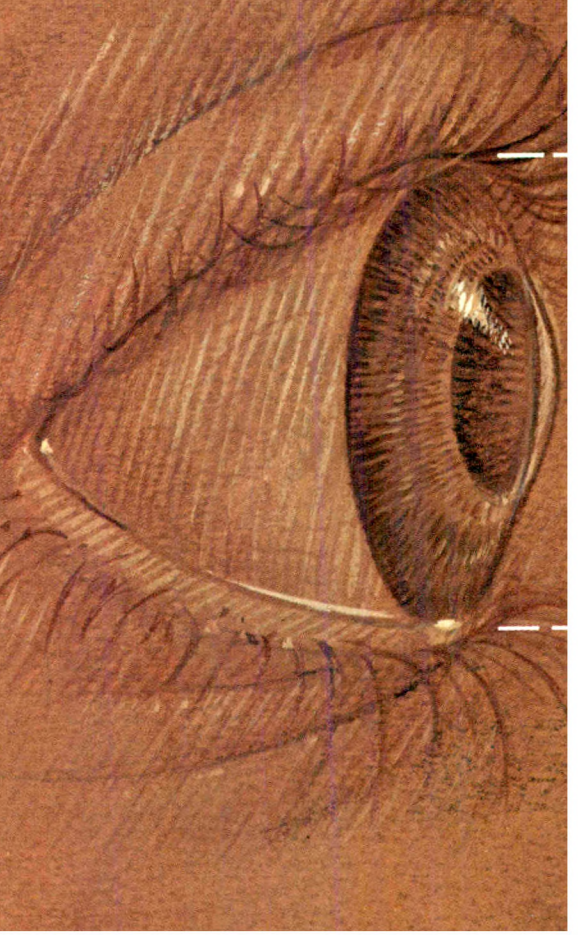

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12.5mm
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three lens diameters
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larger optical zone
See next page for brief summary of prescribing information.

BAUSCH & LOMB SOFLENS® (polymacon) Contact Lenses

BRIEF SUMMARY (For full prescribing information see package circular.)
VISION CORRECTION USE

INDICATIONS: SOFLENS® (polymacon) Contact Lenses are indicated for vision correction use in persons with non-diseased eyes and in aphakia. **CONTRAINDICATIONS:** SOFLENS® (polymacon) Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye with the exception of ametropia and aphakia. **WARNINGS: Abrasions and Infections**—If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrent with lens wear, the lens should be removed immediately and a physician consulted. Infectious corneal ulcers have been reported, usually associated with failure to follow the recommended procedures for care of the lenses. **Aphakic Patients**—Aphakic patients should not be fitted with SOFLENS® (polymacon) Contact Lenses during the postoperative period until, in the opinion of the surgeon, the eye has healed completely. **Lens Sanitation and Handling**—Persons who require only vision correction and who would not, or could not, adhere to the recommended daily-sanitary care of SOFLENS® (polymacon) Contact Lenses or who are unable to place and remove the lenses should not be provided with them. Failure to follow handling and sanitation instructions could lead to serious eye infections which might result in corneal ulcers. Malfunction and rusting of the metal interior of the BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure. Keep the BAUSCH & LOMB® Disinfecting Unit I (ASEPTOR®) clean and dry at all times. **Medicants and Eye Drops**—When the lenses are used by persons requiring only vision correction no ophthalmic solutions or medicants, including conventional (hard) contact lens solutions and eye drops, except BAUSCH & LOMB™ Lens Lubricant should be used by SOFLENS® (polymacon) Contact Lens wearers prior to placement, or while the lens is in place on the eye. Also, no solutions, including conventional (hard) contact lens solutions other than daily cleaner, lens lubricant, saline, and the solution made from the SOFLENS® Enzymatic Contact Lens Cleaning Tablets are to be used on a SOFLENS® (polymacon) Contact Lens when the lens is off the eye. **Wearing Restrictions**—SOFLENS® (polymacon) Contact Lenses, when used only for vision correction, should be removed before sleeping or swimming and in the presence of noxious and irritating vapors. Insufficient lacrimal secretions or hypoesthesia may be restricting factors to the wearing of soft contact lenses. **PRECAUTIONS: Storage**—SOFLENS® (polymacon) Contact Lenses must be stored ONLY in saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in saline solution until it returns to its soft, pliable state which may take as long as forty minutes. Fresh saline solution must be used DAILY for cleaning, storing, and disinfection of lenses. The carrying case must be emptied and refilled with fresh saline solution just before disinfecting the lenses. If using BAUSCH & LOMB™ Salt Tablets to make saline solution, the solution **MUST BE PREPARED FRESH DAILY.** As this saline is not aseptic, it should not be used to clean a lens that is to be replaced immediately on the eye, nor should this solution ever be placed in the eye. If the patient wishes to remove a lens, clean it, or wet it and replace it on the eye, the solution in the carrying case should be used, as it will have been disinfected, or Preserved Saline Solution may be used. **Hygiene**—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses. Cosmetics, lotions, soaps, and creams must not come in contact with the lenses, since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled. **Handling**—A SOFLENS® (polymacon) Contact Lens may be damaged by nicking or tearing if care is not exercised during placement on or removal from the eye, replacing or removing it from the carrying case or in the cleaning process. Lenses must be placed very carefully in the carrying case to avoid damaging the edges of the lenses. **Disinfecting**—Fresh saline solution must be used DAILY for cleaning, storing and disinfection of lenses. If using BAUSCH & LOMB™ Salt Tablets to make saline solution, the solution **MUST BE PREPARED FRESH DAILY.** After removal from the eye, the SOFLENS® (polymacon) Contact Lens must be rubbed gently with Daily Cleaner then rinsed with saline solution to remove mucus and film from the lens surface. The BAUSCH & LOMB® Lens Carrying Case (LENSGARD™) must be emptied and refilled with fresh saline solution just before disinfecting the lenses. In order to remove protein deposits which may form on the lenses, wearers should use the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets according to the directions for use which accompany the tablets. To help remove tear residues and mucus as well as other deposits that tend to accumulate on the lens surface, patients should use Daily Cleaner according to the directions for use which accompany the product. Disinfecting with a BAUSCH & LOMB® Disinfecting Unit I (ASEPTOR®) or II (ASEPTRON™) is necessary to kill microorganisms. If a BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) or II (ASEPTRON™) is not available, the lenses may be disinfected by boiling them in their carrying case in a pan of water for ten minutes. When this boiling method of disinfection is used, the lenses can be damaged if the boiling water is allowed to completely evaporate. The BAUSCH & LOMB® Lens Carrying Case (LENSGARD™) must **always** be **⅔ full** of fresh saline solution before disinfecting and must **always** be tightly closed to prevent leakage of the saline from the case and subsequent dehydration of the lenses. **Fluorescein**—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with sterile normal saline solution and wait at least one hour before replacing the lenses. Earlier replacement may cause the lenses to absorb residual fluorescein. **ADVERSE REACTIONS:** Serious corneal damage may result from wearing a SOFLENS® (polymacon) Contact Lens which has been soaked in a conventional contact lens solution. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation. A lens adheres very rarely to an eye as a result of sleeping with the lens on, or wearing a hypotonic lens. If a lens adheres for any reason, apply fresh saline and wait until the lens moves freely before removing it. Clinical studies indicate that corneal edema, as manifested by symptoms such as rainbows, halos around lights, or foggy vision, may occur in less than 5% of SOFLENS® (polymacon) Contact Lens wearers. If these symptoms occur, the lenses should be removed and professional consultation obtained. Excessive tearing, unusual eye secretions, and photophobia are not normal. If these symptoms occur, the patient should be examined to determine their cause. A faint blue haze, believed to be located in Descemet's membrane, has been reported in the Spokane, Washington area. As yet, the cause is unknown and the phenomenon has not been found elsewhere. The wearers report no subjective symptoms and there is no detectable effect on their visual acuity. There have been approximately 29 cases, and in 10 of these patients the blue haze has cleared or is in various stages of regression. Neovascularization of the cornea has been observed in some aphakic patients fitted with the SOFLENS® (polymacon) Contact Lens, which may require discontinuation of the lens. Medical consultation should be obtained in such an instance.

October 1979

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INTRAOCULAR LENS IMPLANTATION UPDATE

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3625 Park Avenue
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Saturday June 21, 1980

Speakers

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Herve Byron, M.D. .....New Jersey
Miles Galin, M.D. .....New York
Jack Hartstein, M.D. .....St. Louis
Kenneth Barasch, M.D. .....New York
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Registration Fee $125.00 (Residents $50.00)

For information write,
Marvin L. Kwitko, M.D., Program Chairman
5591 Cote des Neiges Rd.
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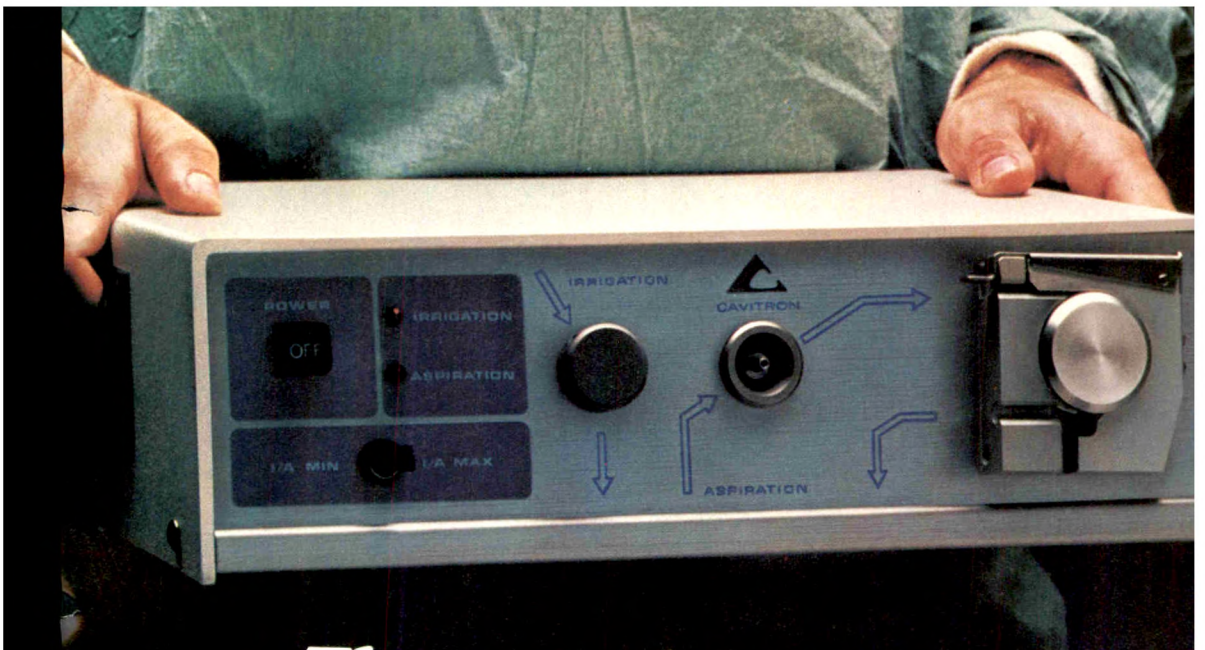
H3T 1Y8



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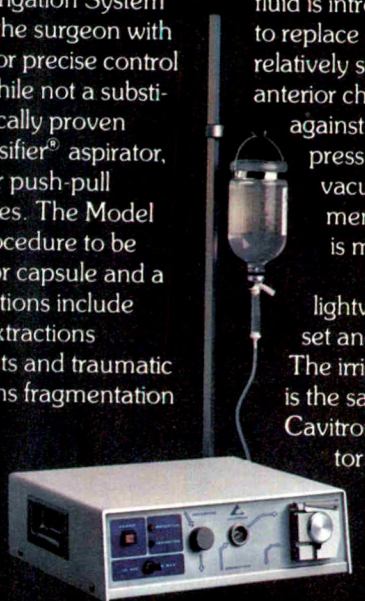

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DEPARTMENT OF OPHTHALMOLOGY
CORNELL UNIVERSITY MEDICAL COLLEGE

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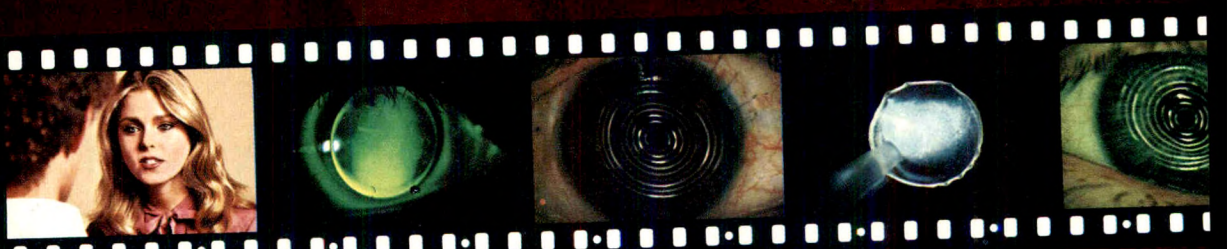

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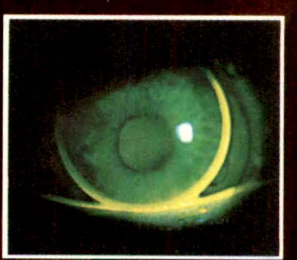

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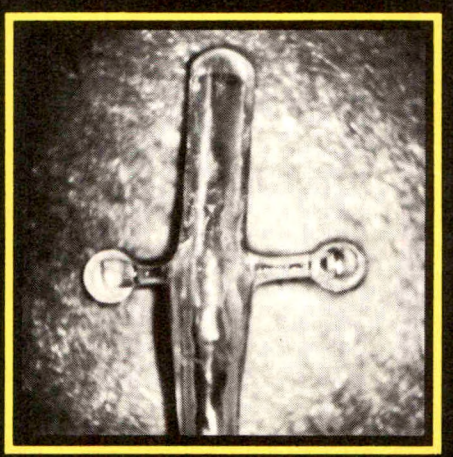

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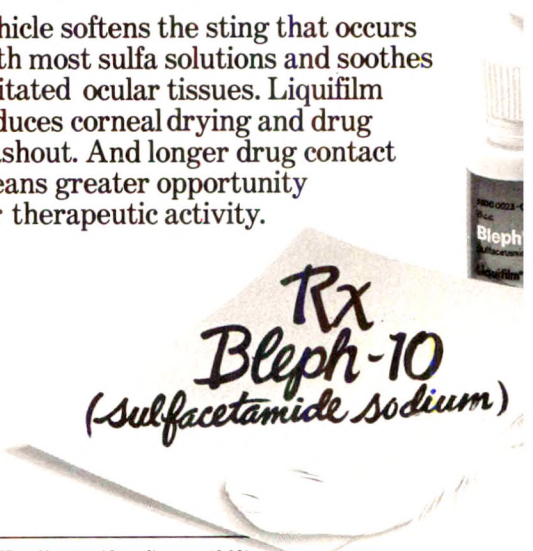

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EXFOLIATION SYNDROME

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The exfoliation syndrome is characterized by the presence of light gray or white flakes clinically most noticeable on the pupillary margin and the anterior lens capsule, but also present on both surfaces of the iris, the zonules, ciliary body, hyaloid, trabecular meshwork, and endothelial surface of the cornea.[1–11] The condition is often associated with glaucoma, and the characteristics of this association have been extensively studied.[12–18] However, apart from the early report of Gradle and Sugar [19] in 1940, the only large study of exfoliation glaucoma in the United States has been by Layden and Shaffer.[9] One remarkable aspect of this latter study was a statement that 93% of the patients who had monocular exfoliation required antiglaucoma treatment in both eyes. This indicates a high prevalence of abnormally high intraocular pressure in the fellow eyes, in which exfoliation had not been detected, and this has led to some speculation that the development of exfoliation glaucoma might commonly require the coexistence of primary open-angle glaucoma.

We re-examined this point by reviewing the records of a group of patients followed up at the Massachusetts Eye and Ear Infirmary Glaucoma Service with exfoliation syndrome. We have also identified factors that might be tested in the future in prospective studies as possible prognostic indicators.

SUBJECTS AND METHODS

We reviewed the records of 74 patients routinely recorded in 1977 as having exfoliation syndrome in one or both eyes. The recorded examinations included slit-lamp examination with pupils dilated, Koeppe gonioscopy, optic disk drawings or photographs, and visual fields. The diagnosis of exfoliation was made by the observation of the characteristic flakes on the lens, iris, or zonules.

Glaucoma was defined, for purposes of this study, as the occurrence of intraocular pressures of 24 mm Hg or higher on at least two occasions, not necessarily accompanied by glaucomatous cupping of the disk or visual field loss. Clinically significant cataracts were those that decreased best corrected visual acuity to 6/18 (20/60) or less.

RESULTS

The patients identified as having exfoliation syndrome in the given time period represented 12% of the current Glaucoma

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Reprint requests to Michael Roth, M.D., Department of Ophthalmology, Medical College of Georgia, Augusta, GA 30912.

Clinic population. There were 38 men and 36 women; the average age was 73 years (range, 53 to 85 years) when exfoliation was first noted. Twenty-eight patients (39%) had bilateral exfoliation syndrome when the condition was first diagnosed. The other 46 patients at first had unilateral exfoliation; but in six of these patients, the exfoliation had become bilateral after six months to 16 years. At the time of review there were 40 unilateral and 34 bilateral cases.

Among the 40 patients with unilateral exfoliation syndrome, eight (20%) had bilateral glaucoma, 25 (62%) had glaucoma only in the eye with exfoliation, and six (15%) had no evidence of glaucoma in either eye (Table 1). One patient had unilateral exfoliation and glaucoma and contralateral neovascular glaucoma without exfoliation. No patient with unilateral exfoliation had glaucoma only in the contralateral eye. In six of the eight patients with unilateral exfoliation but bilateral glaucoma, the glaucoma was more severe and difficult to control in the eye with exfoliation.

Among the 34 patients with bilateral exfoliation syndrome, 22 (66%) had bilateral glaucoma, eight (23%) had unilateral glaucoma, and four (12%) had no glaucoma (Table 2). Six patients with bilateral exfoliation syndrome at the time of review formerly had had unilateral exfoliation that became bilateral. Four of these patients had a history of bilateral glaucoma before developing the exfoliation syndrome in the second eye. No change in the severity of the glaucoma was noted when exfoliation was detected in the second eye. Two of the patients who earlier had unilateral exfoliation that later became bilateral, had glaucoma only in the eye in which the exfoliation was first observed.

TABLE 1

UNILATERAL EXFOLIATION

Condition	No. of Patients
Bilateral glaucoma	8
Unilateral glaucoma	25
Contralateral glaucoma, only	0
No glaucoma	6

TABLE 2

BILATERAL EXFOLIATION

Condition	No. of Patients
Bilateral glaucoma	22
Unilateral glaucoma	8
No glaucoma	4

In the eyes with exfoliation and glaucoma, more than normal pigmentation of the trabecular meshwork was a common finding. Among the 40 patients with unilateral exfoliation syndrome, 19 (47%) had greater pigmentation in the eye with exfoliation. Among the 25 patients with unilateral exfoliation and unilateral glaucoma, 13 (52%) had greater pigmentation in the affected eye. The fellow eyes always had equal or less pigmentation. In cases of bilateral exfoliation and unilateral glaucoma, four of eight patients had significantly greater amounts of pigment in the eye with glaucoma, whereas in the remaining four the amount of pigment in the trabecular meshwork was equal in the two eyes.

Three patients had acute angle-closure glaucoma at the time of initial examination. All three had both exfoliation and cataract in the affected eye. Several patients with exfoliation were noted to have pigment particles[20,21] in the anterior chamber when the pupils were dilated with phenylephrine.

Cataracts were frequently found in our patients with exfoliation syndrome. Although age, therapy, and surgery cloud the analysis, 40% of those with monocular exfoliation in our series had cataract in that eye sufficient to reduce visual

TABLE 3

UNILATERAL EXFOLIATION AND CATARACTS

Condition	No. of Patients
Cataract, exfoliative eye only	16
Cataract, both eyes	0
Cataract, other eye only	2
No clinical cataract	22

acuity, as compared to 5% in the other eye (Table 3). Of the 34 patients with bilateral exfoliation syndrome, 14 (42%) had appreciable cataracts, which were bilateral in nine (27%).

The effect of cataract extraction on intraocular pressure in eyes with both exfoliation syndrome and glaucoma was evaluated in nine eyes of seven patients. None showed lasting reduction of pressure attributable to the operation.

DISCUSSION

Retrospective analysis of the records of patients with exfoliation syndrome in this clinic shows similarities to previously published analyses from other parts of the world. Thus age, sex, incidence of glaucoma and cataract, and effects of cataract surgery are similar to those of Scandinavian and American studies. The prevalence of unilateral and bilateral exfoliation is in agreement with the studies from Scandinavia. We calculated 13% of the patients with unilateral exfoliation later developed exfoliation in the fellow eye, as compared to 15% in Layden and Shaffer's series.[9] However, this phenomenon appears to have been more common in Scandinavian populations.[13,14] We found 40% of the affected eyes with exfoliation to have appreciable cataracts, as compared to 46% in Layden and Shaffer's cases.[9]

One significant difference between our study and that of Layden and Shaffer[9] is that, contrary to their experience, we found evidence of glaucoma to be uncommon in fellow eyes of patients with unilateral exfoliation. This difference is not the result of differences in criteria for glaucoma, because our criteria for diagnosis of glaucoma were actually much less rigid than theirs. The reason for this difference is not clear, but it is noteworthy that the prevalence of unilateral exfoliation as compared to bilateral exfoliation was considerably higher in their series than in most published series,[10,12–14,22,23] or in our own. Because many of Layden and Shaffer's patients were receiving intensive treatment with miotics, some cases of bilateral exfoliation may have gone undetected because of difficulty in obtaining adequate pupillary dilation.

Our observation is that in cases of unilateral exfoliation and glaucoma in the same eye, it is uncommon to have evidence of glaucoma in the contralateral eye. There is evidence of bilateral glaucoma in only 24% of patients with unilateral exfoliation and ipsilateral glaucoma in our series. This suggests that the exfoliation syndrome is in most cases the cause of the glaucoma, and that this is generally a true secondary open-angle glaucoma.

Further supporting this implication for a primary role of exfoliation in causing glaucoma are the results of corticosterioid testing[24,25] and cycloscopy.[26] Corticosteroid testing has indicated that primary open-angle glaucoma and exfoliation glaucoma are separate disease processes. Cycloscopy[26] in cases of overt unilateral exfoliation frequently has indicated the presence of unsuspected early exfoliation in the fellow eye, thus possibly explaining many cases of bilateral glaucoma.

Because the exfoliation process occurs at many intraocular sites, the associated glaucoma might be the result of a primary exfoliation process in the trabecular meshwork,[6] rather than the result of secondary obstruction by pigment or exfoliative material deposited from the aqueous.

Whether pigment deposition is a pri-

mary or secondary factor in the development of exfoliation glaucoma, our study, in agreement with others previously published,[9,10,12] suggests that such trabecular pigmentation may be a prognostic factor relating to the occurrence of glaucoma.

In a brief study Horven[27] observed a 28% incidence of exfoliation in patients with glaucoma in our institution. Our calculated incidence of 12% in this larger study, although lower than in Horven's, is still significant because of its relatively high frequency. We agree with other investigators that exfoliation syndrome is often undetected but is an important cause of open-angle glaucoma. A better understanding of its pathogenesis may offer significant insight into mechanisms of obstruction in other glaucomatous disease of the aqueous outflow pathways.

Summary

We reviewed the records of 74 patients with exfoliation syndrome. Patients with exfoliation syndrome represented 12% of the current Glaucoma Clinic population. There were 40 unilateral and 34 bilateral cases. Thirteen percent of the patients who originally had unilateral exfoliation later developed exfoliation in the fellow eye. Forty percent of the affected eyes with exfoliation had appreciable cataracts.

Evidence for bilateral glaucoma was present in only 22% of the patients with unilateral exfoliation (and ipsilateral glaucoma). The evidence suggests that the exfoliation syndrome is, in most cases, the cause of the glaucoma, and that this is generally a true secondary open-angle glaucoma. Trabecular pigmentation may be a prognostic factor relating to the occurrence of glaucoma.

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ACID PHOSPHATASE IN EYES WITH PSEUDOEXFOLIATION

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Sendai, Japan

Early description by Vogt[1] indicated that pseudoexfoliation was caused by the separation and exfoliation of the pericapsular membrane. A similar mechanism involving the zonular lamella has been proposed by Gifford[2] and Sugar.[3] In contrast, Bussaca's[4] histologic study did not reveal any evidence of capsular dehiscence, which led to the interpretation that it is a deposition of an unidentified material of unknown origin. To reconcile these somewhat disparate opinions and to distinguish the disorder from thermal exfoliation of the lens capsule, the term pseudoexfoliation was introduced by Dvorak-Theobald.[5]

Recent transmission and scanning electron microscopic studies have showed that a true shedding of the superficial capsule may indeed occur.[6,7] Other electron microscopic studies of the pseudoexfoliative materials reveal important features such as the presence of cell organelles,[7] lysosomal vacuoles,[8] and lysosomes[9] scattered within pseudoexfoliative fibrils. Takei and Mizuno[9] noticed abnormal increases in the number of lysosomes in the iris and ciliary body, and Dark, Streeten, and Cornwall[7] proposed the lysosomal role on the formation of the pseudoexfoliative material.

In this study, we examined the correlation between pseudoexfoliation and acid phosphatase, a marker enzyme of the lysosomal enzymes, by using histochemical and biochemical methods.

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MATERIAL AND METHODS

Histochemistry of acid phosphatase—Seven cataractous lenses and seven irises were used in the histochemical study of acid phosphatase. All were initially examined by slit-lamp biomicroscopy after mydriasis. Five of the lenses and irises were obtained from five patients with pseudoexfoliation who had normal intraocular pressure. Two control lenses and an iris were obtained from two patients with senile cataract. Lenses were extracted intracapsularly by cryosurgery without enzymatic zonulolysis. Irises were obtained by peripheral iridectomy. They were fixed for 30 minutes in cold 2.5% glutaraldehyde in 0.1M cacodylate buffer (pH 6.8) immediately after extraction, and rinsed with several changes of the same buffer containing 0.33M sucrose.

For en bloc staining, the lenses with pseudoexfoliation and senile cataract were cut sagittally in half with a razor blade; one half was used for en bloc histochemical examination for acid phosphatase activity, after being incubated in β-glycerophosphate as substrate at 37°C and pH 5.0 for 30 minutes using Gomori's method.[10] A control specimen was incubated in the reaction medium without the substrate. After the incubation, a semicircular incision was made along the postequatorial region under the dissecting microscope, and the posterior capsule, nucleus, and most of the cortex were discarded. The remaining half cup, which consisted of the equator, anterior capsule, epithelium, and superficial cortex, was mounted with glycerine jelly on a glass slide after several cuts at its equator.

For histochemistry of acid phosphatase by light microscopy, the lens and iris

were fixed and washed as previously described. The lens was cut in half, and the nucleus was discarded. The materials were mounted in Tissue-Tek II O.C.T. compound, and sagittal sections of 8 μm thickness were made on a cryostat at −25°C. Sections from each specimen were incubated for acid phosphatase activity by using β-glycerophosphate as substrate at 37°C and pH 5.0 for 30 minutes using Gomori's method.[10] Control sections were incubated in the reaction medium without the substrate.

For electron microscopic histochemistry of acid phosphatase, the method of Miller and Palade[11] was used. After 30 minutes of prefixation in buffered glutaraldehyde solution, the lens was cut into several pieces through the polar axis, and the nucleus and most of the cortex were discarded. The material was then washed several times with cold 0.1M cacodylate buffer (pH 6.8) containing 0.33M sucrose. The pieces were further cut sagittally with a razor blade into slices approximately 10 μm thick. The specimens were incubated for 30 minutes at 20°C in Gomori's medium.[10] Before each experiment, the medium was freshly prepared by dissolving 0.12 g of lead nitrate in 100 ml of 0.05M sodium acetate buffer (pH 5.0) containing 7.5% of sucrose (0.22M) and then slowly adding 10 ml of 3% of β-glycerophosphate. Before use, the mixture was warmed at 60°C for one hour, cooled to room temperature, and filtered to eliminate the slight precipitate. After incubation, the materials were washed twice for one minute in a cold 0.05M sodium acetate buffer (pH 5.0) containing 7.5% sucrose, and postfixed in 1% buffered osmium tetroxide at 0°C for one hour. The materials were dehydrated in graded ethanol, cleared in propylene oxide, and embedded in Epon or Spurr. Most of the materials were then oriented and sagittal sections were obtained. Ultrathin sections were collected on grids, stained with uranyl acetate and lead nitrate, and examined on an electron microscope. Controls were run by omitting the substrate from, or by adding 0.01M sodium fluoride to the incubation medium. Some of the ultrathin sections were observed on the electron microscope without any electron staining.

Biochemical analysis of acid phosphatase in aqueous humor—To assay the activity of acid phosphatase in the aqueous humor, seven eyes with pseudoexfoliation, from patients ranging in age from 65 to 72 years, were selected. As a control group, five eyes of patients with senile cataract but without pseudoexfoliation, ranging in age from 61 to 75 years, were used. They were examined routinely including slit-lamp biomicroscopy to exclude other complications. Approximately 0.2 ml of the aqueous humor was aspirated with a 26-gauge needle and a microsyringe. The aqueous was stored in a freezer until used; 0.1 ml of the aqueous humor with 0.01 ml of 1% of Triton X-100 was incubated in a total volume of 1.0 ml for 20 minutes at 37°C adding 0.1 ml of 1M citrate-sodium citrate buffer at pH 4.5 with 0.2 ml of 50 mM of p-nitrophenyl phosphate as substrate and 0.6 ml of distilled water. The reaction was stopped by adding 10% trichloroacetic acid. After centrifugation, 3.0 ml of 0.5N sodium hydrochloride was added to 1.0 ml of the supernatant. The resulting concentration of p-nitrophenol separated was estimated spectrophotometrically in an alkali-solution at 420 nm by using a spectrophotometer.[11]

Results

Histochemical examination for acid phosphatase—Examination of the flat preparation of the anterior superficial lens of pseudoexfoliation revealed that amorphous flecks of lead phosphate, showing either strong or moderate activity for acid phosphatase, were deposited in the pe-

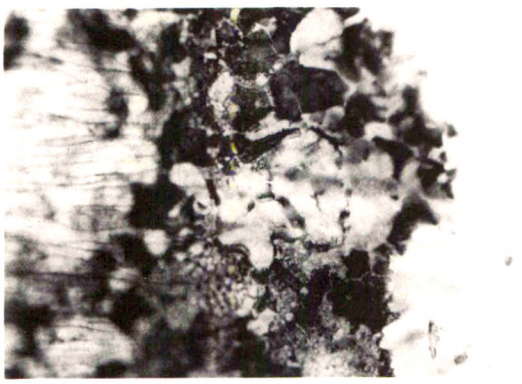

Fig. 1 (Mizuno and associates). Light microscopic histochemistry for acid phosphatase of flat preparation of the lens capsule with pseudoexfoliation. Note reaction product in peripheral zone (×1,000).

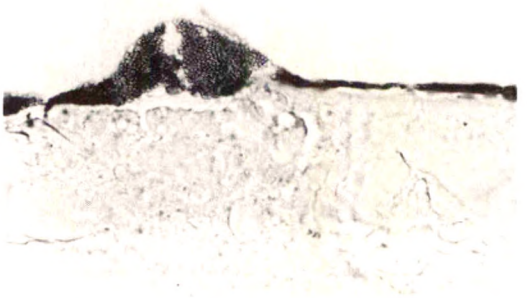

Fig. 2 (Mizuno and associates). Light microscopic histochemistry for acid phosphatase of the lens with pseudoexfoliation. Reaction product is intermingled with pseudoexfoliative materials in peripheral zone (×2,000).

ripheral zone on the lens surface (Fig. 1). However, no appreciable reaction products were encountered in the central disk.

Histochemistry for acid phosphatase in cryostat sections of the peripheral zone also revealed conspicuous activity of the enzyme in the mass of pseudoexfoliative material lying on the lens capsule (Fig. 2), whereas only a few reaction products appeared in the central disk. Lead precipitate was also found dispersed within the pseudoexfoliative material attached to the posterior surface of the iris (Fig. 3). In control preparations, no deposits of lead precipitate were observed on the surface of the lens capsule.

Electron microscopic observation of the iris and lens capsule of eyes with pseudoexfoliation revealed an extraordinary variety in localization and intensity of acid phosphatase reaction (lead phosphate). There were two types of iris pigment epithelial cells on the iris. The first type consisted of cells of which the cell membrane facing the posterior chamber was well preserved and continuous, though disorganization of endoplasmic reticulum and vacuolization had already taken place in the cytoplasm. In these cells, reaction products of acid phosphatase appeared sharply localized in a number of phagolysosome concentrated in the posterior part of the cell. Consequently, pseudoexfoliative fibrils adjacent to the cell rarely contained acid phosphatase positive products (Fig. 4). The second type consisted of the pigment epithelial cells of which the cell membrane facing the posterior chamber had partially disappeared and was discontinuous, and a number of vacuoles increased in the cytoplasm. The reaction products were scattered in and out of the cells. Additionally,

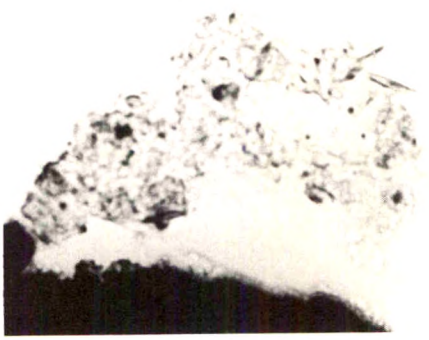

Fig. 3 (Mizuno and associates). Light microscopic histochemistry for acid phosphatase of the iris of patient with pseudoexfoliation. Reaction product is dispersed within pseudoexfoliative materials that are attached to the posterior surface of the iris (×1,000).

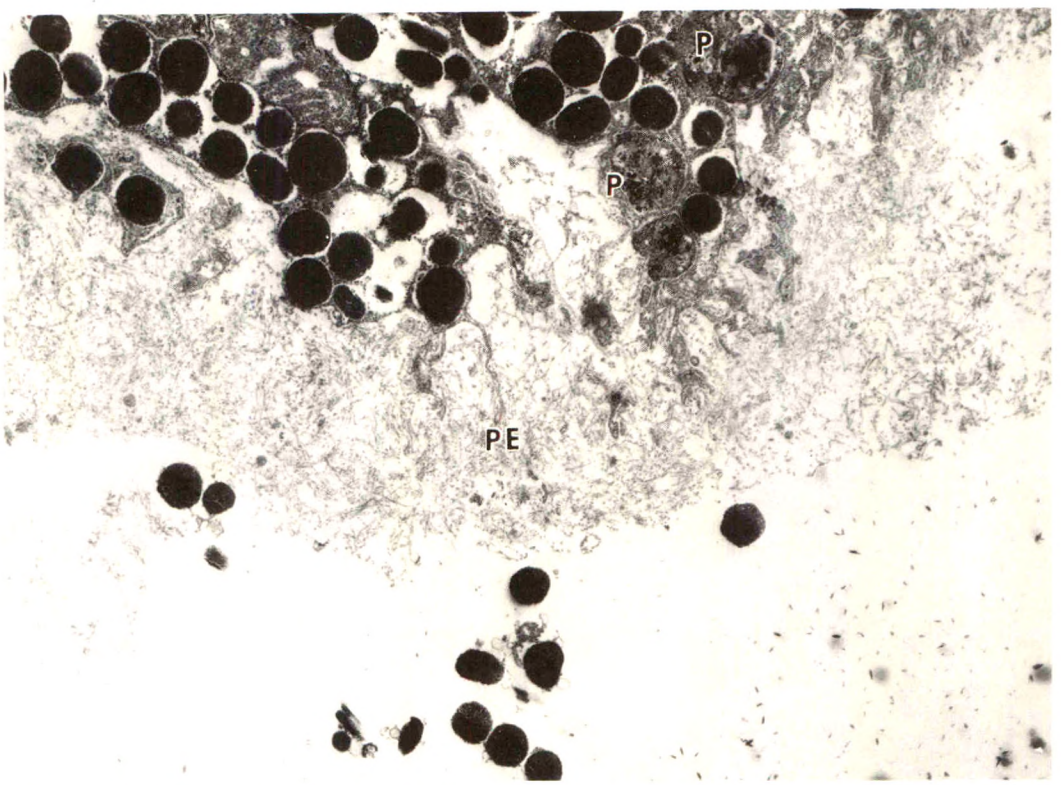

Fig. 4 (Mizuno and associates). Electron microscopic histochemistry for acid phosphatase of the iris with pseudoexfoliation. Lead precipitate is seen in a phagolysosome (P) concentrated in the posterior half of cytoplasm. Cell membrane is well preserved to prevent dispersion of acid phosphatase positive particles into pseudoexfoliative fibrils (PE) (×6,600).

the limiting membrane of phagolysosome in the cells also became obscure in part, and particles of lead phosphate were likely to be released from it, intermingling with pseudoexfoliative fibrils adjacent to the cells (Fig. 5).

The distribution of acid phosphatase positive precipitates in the lens capsule of pseudoexfoliation differed significantly between the central disk and peripheral zone. In the central disk, only occasionally a slight precipitate formed in pseudoexfoliative fibrils surrounding melanin containing phagolysosome, whereas other pseudoexfoliative fibrils rarely contained the precipitates (Fig. 6). The peripheral zone frequently adhered to the posterior surface of the pigment epithelial cell, resulting in pigmented pseudoexfoliative material on the extracted lens. In such cases, fine dense precipitates appeared within pseudoexfoliative fibrils that firmly adhered to the group of pigment granules separated from the iris pigment epithelium. The precipitates also appeared in and out of phagolysosome that was possibly separated from the pigment epithelial cells. However, acid phosphatase positive precipitates were rarely seen in pseudoexfoliative fibrils distant from the pigment granules (Fig. 7). In the peripheral zone of another case of pseudoexfoliation, the product of acid phosphatase reaction mainly appeared in a large aggregate within phagolysosome on the lens capsule. The dispersed product also appeared within pseudoexfoliative fibrils and pigment granules that were closely

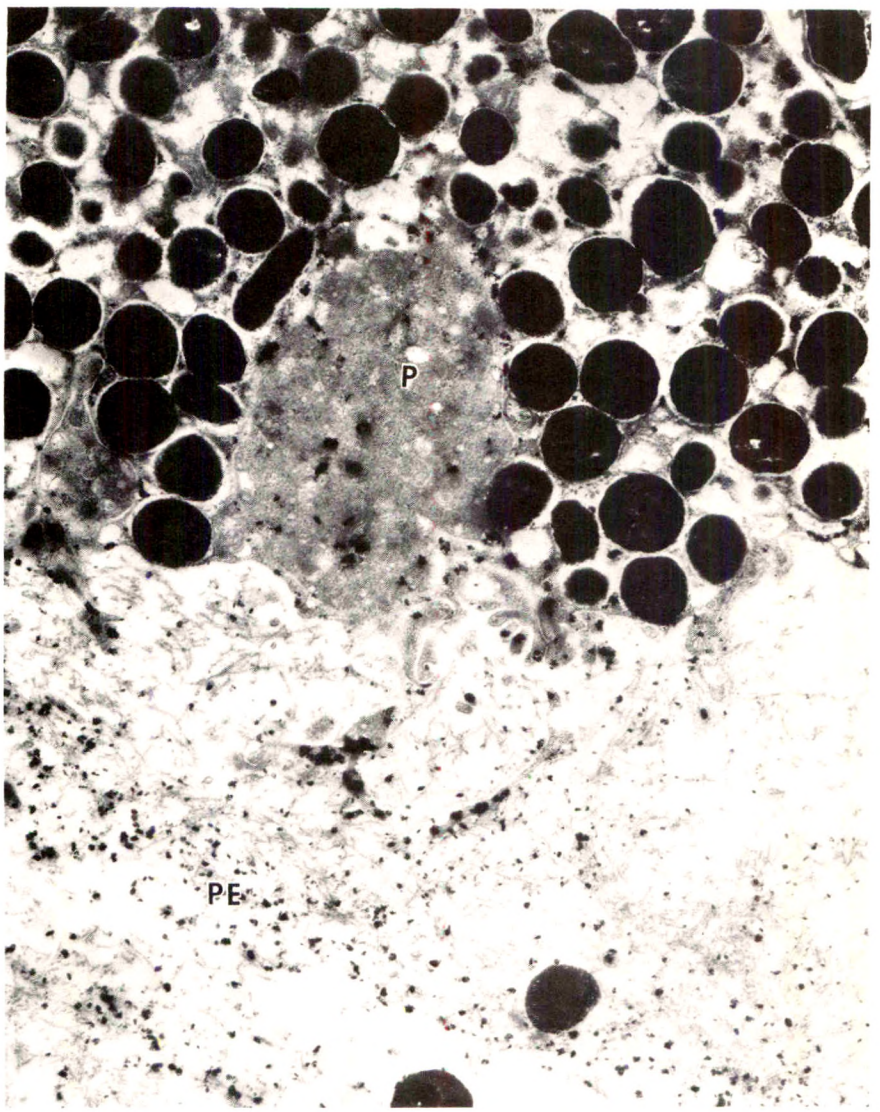

Fig. 5 (Mizuno and associates). Electron microscopic histochemistry for acid phosphatase of the iris with pseudoexfoliation. Lead phosphate is seen in and out of phagolysosome (P) of which limiting membrane is ruptured, so that it intermingled with pseudoexfoliative fibrils (PE) (×6,600).

attached to the lens capsule. These situations were clearly proven in electron microscopy processed without any counterstaining (Fig. 8).

In specimens of normal subjects, the acid phosphatase positive product was limited to a small number of lysosomes in the iris pigment epithelium and lens epithelium. In controls that omitted the substrate from the medium or which added sodium fluoride to the medium, either none or a significantly reduced number of lead phosphate precipitates were found.

Biochemistry of acid phosphatase—The enzyme activity in the aqueous humor was expressed as the amount of p-nitrophenol released in 0.1 ml of the aqueous humor with incubation for 60

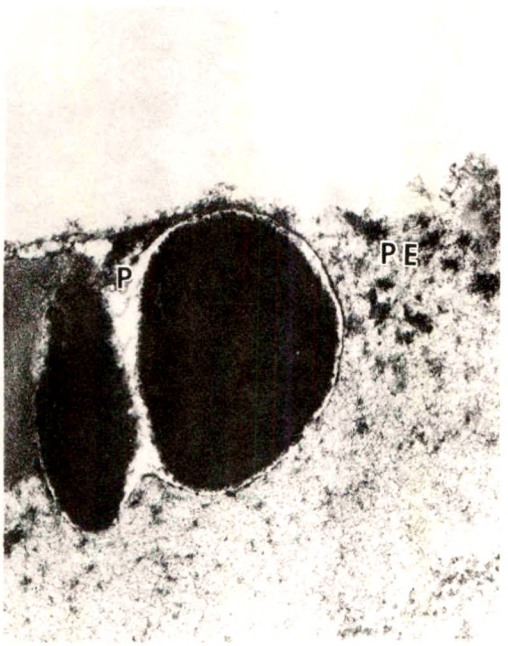

Fig. 6 (Mizuno and associates). Electron microscopic histochemistry for acid phosphatase of the central disk of the lens with pseudoexfoliation. Lead phosphate slightly precipitates within pseudoexfoliative fibrils (PE) around melanin containing phagolysosome (P) (×30,000).

minutes at 37°C. The average value of seven eyes with pseudoexfoliation was 127 ± 49.6 μg/ml (mean ± S.D.), whereas that of five eyes with senile cataract was 38.4 ± 4.8 μg/ml (Table). The latter is considered to be within the error of measurement. Thus, the acid phosphatase activity was significantly higher ($P < .005$) in the aqueous humor of eyes with pseudoexfoliation.

Discussion

Our histochemical and biochemical observations have shown the presence of acid phosphatase, a marker enzyme of lysosomal enzymes, in the pseudoexfoliative material of the lens capsule and iris, and in the aqueous humor of patients with pseudoexfoliation. These observations, in part, support the previous study[9] in which we predicted from electron microscopic observations that the original site of pseudoexfoliation might be in the iris, ciliary process, and zonule, and that lysosomes might account for the pathogenesis of pseudoexfoliative disease.

Lysosomal enzymes have an important extracellular as well as intracellular role in the digestion of macromolecules. The high activity of lysosomal enzymes such as acid phosphatase, β-glucuronidase,[12] cathepsin B,[13] cathepsin D,[14] and acid lipase[15] have been detected in the iris and ciliary body of the bovine eye, but not in the aqueous humor. It is assumed that lysosomal enzymes are barely detectable in the aqueous humor under normal conditions even in cataractous eyes. Under some pathologic conditions, such as pseudoexfoliation, it is not unreasonable to assume that lysosomal enzymes may appear in the aqueous humor.

A significant increase in acid phosphatase in the aqueous humor of eyes with pseudoexfoliation is of interest when considering that the pseudoexfoliative material attaches to the surfaces that are facing the aqueous humor; Davenger[16] found it attached to the iris, to the ridge of the ciliary processes, to the zonules, and along the radial strips on the anterior hyaloid surface.

With reference to the release of acid phosphatase from the iris and ciliary body into the aqueous humor, separation of lysosomes from the epithelial cells is suggested. The present electron microscopic histochemical study has shown acid phosphatase activity not only in phagolysosome but also within pseudoexfoliative fibrils. Additionally, the frequency of reactive sites and intensity of reaction of acid phosphatase is likely more significant in the following: (1) pseudoexfoliative fibrils nearer to the disorganized pigment epithelial cell of the iris, and (2) pseudoexfoliative fibrils nearer to the ruptured phagolysosome whether it is in or out of the pigment epithelium. Thus, there is a definite association between lead phosphate over

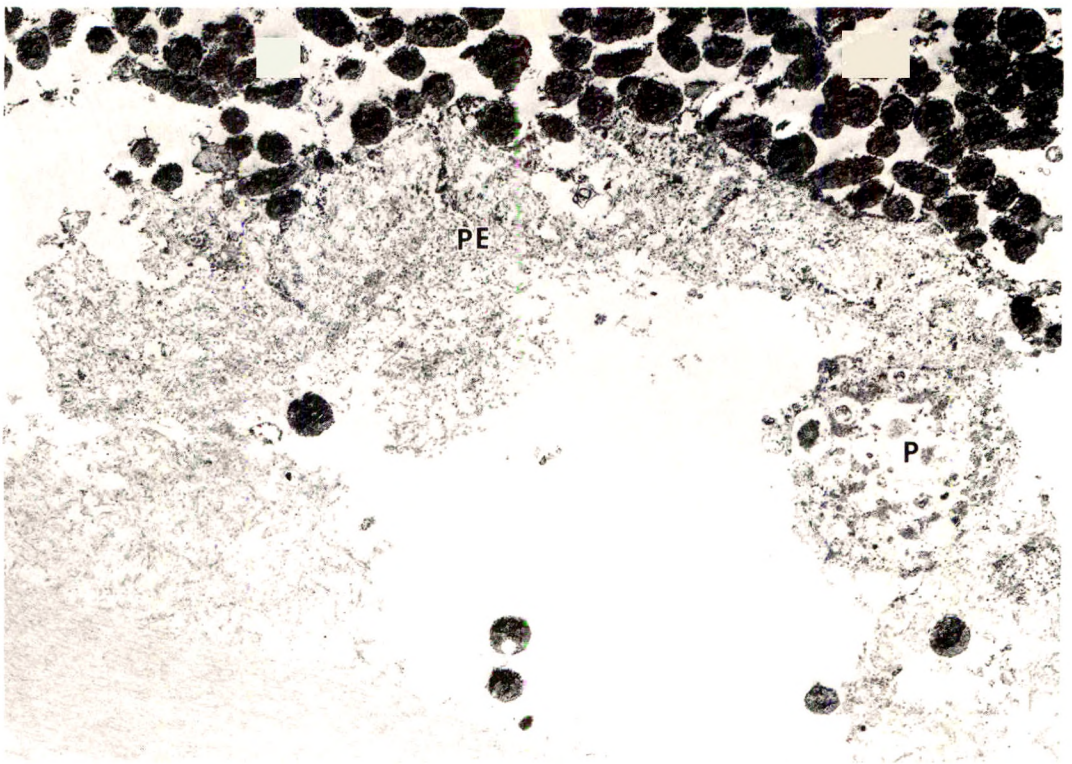

Fig. 7 (Mizuno and associates). Electron microscopic histochemistry for acid phosphatase of the lens with pseudoexfoliation. Lead phosphate is seen in pseudoexfoliative fibrils (PE) near pigment granules and broken phagolysosome (P) separated (×6,600).

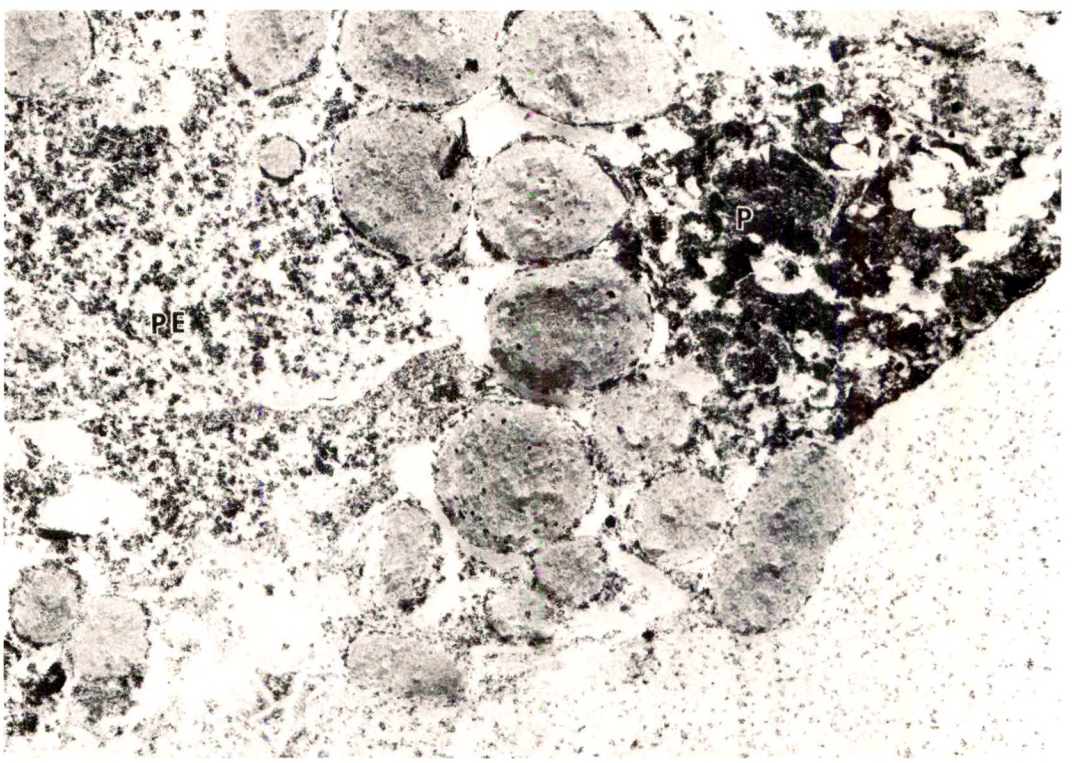

Fig. 8 (Mizuno and associates). Electron microscopic histochemistry for acid phosphatase of the lens with pseudoexfoliation without counterstaining. Lead phosphate is aggregated in phagolysosome (P) and dispersed within pseudoexfoliative fibrils (PE) (×20,000).

TABLE

ACID PHOSPHATASE ACTIVITY IN AQUEOUS HUMOR WITH AND WITHOUT PSEUDOEXFOLIATION*

Case No.	μg p-Nitrophenol Released/60 min 37°C/ml	
	PE Disease	Control
1	240	36
2	108	36
3	96	36
4	120	36
5	96	48
6	144	—
7	84	—
Mean ± S.D.	127 ± 49.6	38.4 ± 4.8

*PE designates pseudoexfoliation.

pseudoexfoliative fibrils and disorganization of the pigment epithelium and phagolysosome. The same lysosome and lysosome-like vacuoles were frequently found in the other parts of the anterior segment in eyes with pseudoexfoliation.[8,9,16,17] Therefore, the lysosomal limiting membrane in the pigment epithelium of the iris or ciliary body, or both, may be broken down in pseudoexfoliation, consequently releasing acid phosphatase into the aqueous humor. However, we do not know whether or not the atrophic process of the pigment epithelium in the iris and ciliary body is the primary or secondary event of pseudoexfoliation. However, a lysosomal enzyme may be directly or indirectly involved with some particular pathologic processes of this disorder.

SUMMARY

We studied the activity of acid phosphatase in the anterior segment of the eye with pseudoexfoliation histochemically and biochemically. Light and electron microscopic histochemistry revealed lead precipitates indicating acid phosphatase activity in pseudoexfoliative materials. Biochemical assay for acid phosphatase was significantly higher in the aqueous humor of eyes with pseudoexfoliation than in that of cataractous eyes without pseudoexfoliation.

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ULTRASONICALLY ACCELERATED RESORPTION OF VITREOUS MEMBRANES

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In the management of vitreous hemorrhage the removal of blood elements and the disruption of physical bonds between the vitreous and retina have been beneficial not only in clearing opacities that reduce vision, but also in interrupting the sequence of disease that produces retinal destruction and detachment.[1,2] At present, means of accomplishing the removal of these blood elements and the interruption of physical attachments are limited to surgical methods or enzymatic therapy as there is no accepted systemic or other noninvasive technique to produce the desired changes. High intensity ultrasound, which can be focused selectively within the eye, is a promising modality for treating intravitreal substances that threaten vision.

The clinical applications of ultrasound in ophthalmology have thus far been confined to diagnostic visualization systems for conveying anatomic information. At the low intensities used for diagnosis, no known alterations occur in tissue structure.[3,4] At high intensities, ultrasound can be used to actively modify tissue structures. High-frequency ultrasound can be focused to submillimeter spot sizes and delivered to sites inaccessible to other therapeutic modalities such as intense light. It thus offers exciting, often unique, opportunities for noninvasive treatment of a variety of ocular and orbital conditions. We have previously examined several applications such as the induction of controlled chorioretinal lesions and have provided the data base needed to avoid deleterious side-effects such as cataractogenesis.[5–8]

Vitreous hemorrhage followed by membrane formation is a primary cause of blindness and results most commonly from diabetes and trauma. Diabetic retinopathy is one of the leading causes of blindness in the United States.[9] The sequence from vitreous hemorrhage to retinal detachment and proliferative disease has therefore been the subject of intensive research and experimentation. Despite extensive studies of the relationship between hemorrhage (blood elements) in the vitreous, and vitreoretinal toxicity and progressive retinal disease (pioneered by Cibis[10]), neither is the progression fully understood, nor is the disruption easily accomplished.

Until recently, opacities and disease of the vitreous body, despite their serious effects on vision and even the health of the eye, could not be therapeutically altered. The clinical advance of vitrectomy has improved the poor prognosis for vitreous disease, and has led to a widespread use of such surgery to correct many vitreous abnormalities. Vitrectomy, however, is a serious assault on the eye, associated with significant risks.[11] These risks include iatrogenic retinal detachment, repeated hemorrhages, corneal decom-

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pensation, cataracts, neovascularization, glaucoma, and phototoxicity.[12,13] Additionally, purely technical limitations of the procedure itself may preclude the desired beneficial results. Other therapeutic procedures (for example, injection of specific enzymes) are limited to specific vitreous abnormalities and are frequently not fully effective. Moreover, vitrectomy or other therapeutic procedures are generally delayed to permit natural resorption processes to begin. During this waiting period, other degenerative changes may occur. For example, a vitreous hemorrhage may cause vitreous traction membranes to form[14] or exudates occurring after uveitis may promote periretinal proliferation.

We describe a series of in vivo experiments that show the clinical potential of intense ultrasound as a noninvasive, precisely controlled means of accelerating the resorption of vitreous membranes which thereby halts the progression toward retinal detachment. This evaluation was made possible by the development of a model for the production of experimental vitreous membranes.

Material and methods

Insonification system—The system for delivering calibrated exposures of focused, high-intensity ultrasound to confined regions of the rabbit eye was described in a previous report.[8] In the present study, this system was used, but the therapeutic transducer had a different configuration. A central circular aperture was cut in the transducer that was fabricated from a spherically curved segment of ceramic material. The central aperture housed a focused diagnostic transducer that can be used for aiming the therapeutic beam (Fig. 1). Acoustic coupling between the eye and the transducer was supplied by degassed, distilled water contained in the conical housing seen in Figure 1. Pilot experiments in the rabbit eye showed that vitreous membranes could be imaged with the central 10-MHz transducer operated in the diagnostic, pulse-echo mode. Alignment fixtures on the transducer assembly can be used to adjust the relative orientations of the two transducers such that their beams are collinear and confocal.

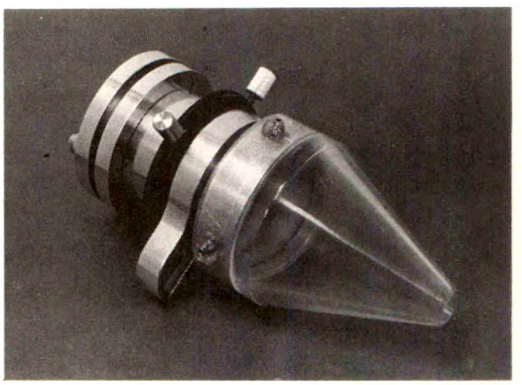

Fig. 1 (Coleman and associates). The transducer assembly with therapeutic transducer installed. The Lucite cone holds degassed water that provides a low-loss path between the transducer and the eye.

The therapeutic transducer was used in all procedures described in this report even though the diagnostic system was not fully operational. The presence of the central aperture in the therapeutic transducer alters the generated beam pattern to some degree. Schlieren photography studies showed the beam produced by this transducer that was operated at a frequency of 9.72 MHz. The beam shape was in excellent agreement with theoretical predictions for a focused annular transducer whose inner diameter (20 mm) is half of its outer diameter (40 mm). Theory predicts an elevation of side-lobe intensities and a narrowing of the main lobe of the beam.[15] In the present case, the focal spot size (at the 3-dB or half-power points) was 0.35 mm. The transducer was capable of generating focal spot intensities exceeding 1,000 W/cm^2.

The therapeutic transducer was used to generate both continuous wave and

pulsed ultrasound. Intensity levels were determined by radiation-force methods and beam-profile information. In specifying intensities, this report refers to the spatially averaged intensity generated within the 3-dB focal spot. When pulses are used, peak intensity refers to the temporal peak intensity level that is reached during an ultrasonic pulse; average intensity refers to the temporal average existing between the time the first pulse is initiated and the last pulse cycle is terminated. All reported pulsed conditions had a 50% duty cycle; that is, the duration of a pulse was equal to the quiescent period between pulses. Accordingly, the peak intensity is equal to twice the average intensity for pulsed exposures. Additionally, the small attenuation losses in intervening tissue have been calculated and included in the reported intensities.

Experimental procedures—Extensive initial studies were performed in vitro. Excised bovine vitreous was injected with platelet-rich plasma that formed pseudomembranes. Pilot studies of pulsed and continuous wave insonification regimens were done to ascertain the energy levels required to move and disrupt membranes. These data were then used for the following in vivo studies.

The in vivo experiments used vitreous membranes that were produced by injection of 0.1 ml of platelet-rich plasma into the vitreous body of albino rabbit eyes.

Insonification of in vivo membranes was performed in the proptosed globe of the anesthetized rabbit.[8] The proptosed eye of the rabbit was surrounded by a bath of saline solution at 37° C. The transducer assembly was positioned with a micrometer stage so that the focused ultrasound beam traversed the lateral scleral wall and intercepted the center of the vitreous membrane. Care was taken to prevent passage of the beam through the crystalline lens that would introduce significant acoustic refraction and absorption. Each globe was treated with five insonification episodes. The transducer was repositioned in increments of 1 mm between each of the five episodes so that the beam intercepted different parts of the membrane. Each episode in a single globe used the same intensity, the same ultrasound modality, and lasted five seconds. Membranes were subjected to insonification either one day or eight days after injections of platelet-rich plasma. The entire insonification procedure was completed within ten minutes. The membrane was observed through the dilated pupil during insonification and any movement of the membrane was noted.

In the present study, in vivo membranes were prepared in 55 globes. Thirty-six globes were treated with ultrasound, ten globes served as controls, and four served as shams. These globes were observed until total resorption of the membrane had occurred or until the rabbit was killed. Many rabbits were killed before complete resorption for histologic study at specified time periods; these included five untreated animals whose globes were prepared for histology shortly after formation of the membranes.

Two series of in vivo insonification experiments were conducted. In the first series of experiments, continuous wave and pulsed ultrasound at pulse repetition frequencies (prf) of 10 Hz and 1,000 Hz were used with high peak intensities (exceeding 1,000 W/cm^2). These experiments were conducted in order to assess the relative effectiveness of each exposure modality.

The second series of in vivo insonifications was performed to determine the effect of ultrasound intensity on the time course of membrane resorption. The experiments were conducted as described previously, except that only pulsed ultrasound, 10 Hz prf, was used and a wider range of intensities was applied. A pulse repetition frequency of 10 Hz was select-

ed because it permitted excellent visualization of membrane movements that occur during insonification.

Sham globes received the same treatment as treated globes (that is, the globe was proptosed, and the like), except that the therapeutic transducer was not energized. Control globes received no further treatment after the injection of platelet-rich plasma.

All globes were examined at least once a week by direct and indirect ophthalmoscopy. All membranes were photographed regularly with a handheld fundus camera. Their general appearance was also sketched and annotated to ensure complete documentation.

Results

A vitreous membrane formed after each injection of platelet-rich plasma. The membrane was seen immediately after the injection as a white or cloudy mass consisting of interconnected spheroid clumps, sheets, and strands. Except for a gradual diminution in size during resorption, there were no changes in position or orientation of the membranes after their initial formation.

Control and sham membranes showed progressive resorption with time; eight of these untreated membranes were followed up to complete resorption. The initial stages of resorption were rapid and involved sites where the membrane was thinnest; denser portions required longer periods to resorb.

During resorption, the membrane remained in the same configuration but became progressively thinner until only thin cords, diaphanous sheets (veils), or small clumps remained. This stage was followed by the appearance of localized haze in which specific elements could no longer be identified. The haze diminished progressively and resorption was judged to be complete when the central vitreous was clear. In some cases, a few, small, discrete particles remained, usually in the inferior portion of the vitreous. These particles were not organized into cords or veils and did not fall along the visual axis. Thus, it was concluded that they posed no clinically significant problem and resorption was graded as complete.

A total of 29 globes were subjected to insonification and followed up until complete membrane resorption was observed. During insonification, the membrane could be clearly visualized through the dilated pupil. The membranes were often displaced during ultrasonic exposure, the displacement occurring in a direction away from the transducer. Membrane displacement was noted during 90% of all pulsed exposures and was most easily seen with pulsed ultrasound at 10 Hz prf. Upon termination of the exposures, the membranes returned to their initial position and no immediate change from appearance before exposure was evident, except in two globes, where the membranes were severed during insonification.

Treated membranes were followed up with the same techniques applied to untreated membranes. The resorption process followed stages that paralleled those seen in untreated membranes with the primary exception being a significant reduction in the time required for complete resorption.

The average time for complete resorption for all treated membranes was 62% of the time required by untreated membranes. Exposure to the highest intensity used in the study reduced resorption time to 49% of the control time, whereas exposure to the lowest intensity reduced this time only marginally to 94% of the control time.

Fundus photographs of the stages of resorption in a globe treated with high intensity are shown in Figure 2. Initially, resorption began at the thin peripheral sections of the membranes as in controls,

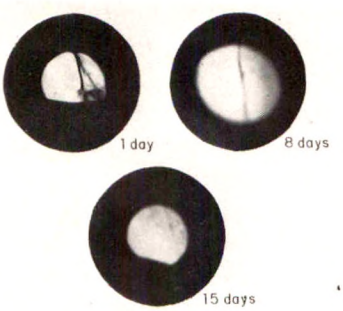

Fig. 2. (Coleman and associates). Fundus photographs of the progress of resorption of a typical in vivo vitreous membrane exposed to high intensity ultrasound.

but in globes subjected to insonification resorption was also initiated in the section of the membrane that was intercepted by the beam. After this stage, a further diminution in size occurred that progressively included the denser portion of the membranes. The last regions to be resorbed were situated superiorly, in the region of the injection site, and posteriorly, at the region of the medullary ray. Resorption occurred last in the vicinity of the optic nerve head if the membrane extended that far. The initial, rapid phase of resorption occurred in the same time period for both treated and untreated globes ranging from two to 14 days, ten days on the average. The treated membranes, however, lost a greater proportion of their bulk in that initial period of breakdown, so that the overall resorption time was less than for untreated membranes.

The times required for complete membrane resorption are listed in the Table. (This table does not contain data from globes removed for histology before complete resorption.) For untreated cases, resorption time ranged from 15 to 55 days with an average of 34 days and a median of 35 days.

The data base can be discussed in terms of two experimental groups. The first group consists of Categories 1 to 5 where high intensities were applied; specifically, this group includes all membranes exposed to peak temporal intensities greater than 1,000 W/cm^2. In all of these instances, resorption time was reduced significantly with respect to untreated cases. The average resorption time in this group is between 49 and 57% of the 34 days that characterizes the untreated population. The overall average resorption time for this group is 17 days or 50% of the control resorption time.

The second experimental grouping con-

TABLE

RESORPTION OF VITREOUS MEMBRANES

Category No.	Insonification Regimen	Age of Membranes when Treated (days)	No. of Globes	Temporal Intensity (W/cm^2)		Average Days to Complete Resorption After Injection
				Peak	Average	
1	Continuous wave	1	4	1,343	1,343	16
2	Continuous wave	8	4	1,240	1,240	23
3	1 kHz pulsed	1	5	1,136	568	20
4	1 kHz pulsed	8	3	1,025	513	19
5	10 Hz pulsed	1	6	1,124	562	18
6	10 Hz pulsed	1	2	902	451	27
7	10 Hz pulsed	8	2	820	410	15
8	10 Hz pulsed	1	3	333	167	32
9	Controls	—	6	—	—	33
10	Shams	—	2	—	—	35

sists of Categories 5 to 8 in which pulsed ultrasound was applied at a 10-Hz prf, using a range of peak intensities between 1,124 and 333 W/cm². In this group, intensities below 1,000 W/cm² facilitate resorption to variable degrees. On the average, these lower intensities produce a reduction in resorption rate to 23 days, which is 67% of the control rate.

At lower intensities (but still many times greater than intensities used in diagnostic ultrasound), it was not uncommon to find that resorption rates varied widely within a single membrane. One such case is shown in Figures 3 and 4 of two sections of a membrane that was treated at a 10-Hz prf and a peak intensity of 164 W/cm². One large region of the membrane was completely resorbed in nine days, whereas the other region persisted until 90 days, at which time the animal was killed. (As this membrane did not go on to complete resorption, it is not included in the Table.) These large disparities in resorption rates were not seen in insonification episodes at high intensity.

The age of membranes at insonification is not consistently indicated as a significant factor in influencing resorption rates. The two membranes treated at 10 Hz after eight days in the eye (Category 7), resorbed significantly more quickly than the two membranes that were treated at similar intensity levels after only one day in the eye (Category 6). A similar comparison, however, at 1-kHz insonification modality shows only minimal difference in resorption rate for eight-day old and one-day old membranes (Categories 3 and 4).

Most of the focal-spot intensities used in these experiments exceeded the threshold values we have reported for chorioretinal lesion formation. For five-second exposures, the threshold occurs at a temporal average intensity of 150 W/cm², and a peak temporal intensity of 300 W/cm² for the pulse factors used here. In this study with peak intensities above 1,000 W/cm², chorioretinal lesions were produced in 13 individual exposures at high intensity levels with both continuous wave and pulsed modalities. When lesions occurred, they were situated posterior to the membrane and grouped (if more than one) in close proximity to each other. The course of these lesions was identical to those described in a previous publication.[8] No chorioretinal lesions were seen in exposures using peak intensities below 900 W/cm². In the present experiment the

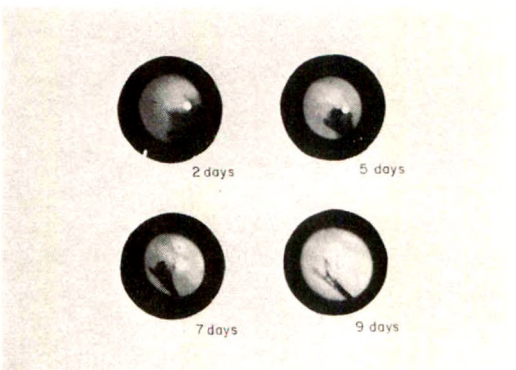

Fig. 3 (Coleman and associates). Fundus photographs showing the progress of resorption of the treated portion of an in vivo vitreous membrane exposed to reduced intensity.

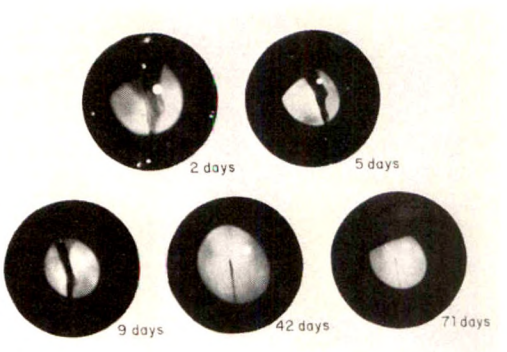

Fig. 4 (Coleman and associates). Fundus photographs showing the progress of resorption of the untreated portion of an in vivo vitreous membrane exposed to reduced intensity.

focal point of the beam was not situated on the retina but near the midvitreous locations of the membrane.

The microscopic appearances of membranes immediately after insonification did not reveal any obvious qualitative or quantitative differences from those that were untreated (unpublished data). The absence of detectable differences could be the result of the acellular, amorphous nature of the midvitreal membranes and to the random disruptions created by histologic techniques on the vitreous. Breaks observed in the membranes could not be differentiated as to cause, whether by ultrasonic disruption or by preparation artifact.

Discussion

In interpreting the numeric data from these studies, there are several considerations. The membranes created by injection of platelet-rich plasma show properties which are, for the most part, repeatable. However, occasional variations are seen. For example, portions of one untreated membrane remained for 360 days at which time the animal was killed.

This animal was atypical and has been excluded from the data base. Additionally, the end point for this study, that of total membrane resorption, was chosen because it is a less subjective measure than other end points. This end point provides a conservative measure of the usefulness of ultrasonic treatment because the bulk of a treated membrane was often resorbed quickly, whereas small remnants persisted for longer periods.

The primary conclusion to be drawn from these experiments is that intense ultrasound can significantly facilitate the resorption of intravitreal membranes. This conclusion has obvious clinical implications and raises a number of questions for consideration in assessing the clinical applicability of this technique. The topics of prime importance are the relationship between the membrane model with those found in humans, the mechanism governing the facilitated resorption, and optimum modes of exposure under clinical situations.

We observed the relationship between the platelet-rich plasma-induced membranes and those found in humans (unpublished data). Briefly, the experimental membranes differ from those clinically encountered primarily because of their spontaneous resorption in usually short intervals (34 days). However, similarities also include the occasional development of traction retinal detachments and histologic evidence of fibroblastic activity. Localized traction detachments involved the membrane formed initially by the injection of platelet-rich plasma and a secondary posterior membrane that resulted from the fibroblastic activity. In some cases, the secondary membrane alone seemed to produce the detachment. The differences preclude a detailed extrapolation of experimental results to the human situation. However, the similarities and the significant increases in resorption rates after insonification warrant continued studies.

Specifically, early insonification of membranes produced more rapid resorption that removed the matrix for traction on the retina and thereby eliminated the possibility of retinal detachment. No retinal elevation or detachment occurred in treated rabbit eyes; as compared to an occurrence of retinal detachment in 15% of untreated eyes. Additionally, insonification may inhibit fibroblastic activity that is responsible for the development of the secondary membrane. Additional study is necessary to ascertain the optimum timing for treatment, but the data do suggest that interruption of the membranes in this preproliferative stage, lessens later morbidity. Insonification levels and regimens for membranes already in the proliferative phase are still unknown.

The mechanism responsible for accel-

erated resorption is not clear. Companion studies in vitro showed an immediate, gross disruption of membranes formed in excised bovine vitreous. In contrast, in vivo studies rarely resulted in immediate, permanent effects; such effects were noted in only two globes. The differences between in vitro and in vivo results call to mind those found by Donn,[16] regarding vitreous liquifaction that was accomplished only under in vitro conditions. We believe that mechanical effects are most likely the cause of increased resorption rates. Mechanical disruptions on a smaller scale than seen in vitro could render the membrane more susceptible to resorption by increasing the surface area available for phagocytic activity and by weakening structural linkages. The observed accelerated resorption of only the treated portions of membranes exposed to reduced intensities suggests a local instead of a general mechanism. Although gross vitreous liquifaction was not observed, intense ultrasound might create tunnels and pathways through the vitreous and membrane, thus permitting macrophages to gain easier access to treated portions of the membrane.

The usefulness of certain exposure modes in hastening resorption also suggests a mechanical effect. The high peak intensities used were kept within 15% of a common value and revealed no sizeable difference in usefulness (see the Table, Categories 1 to 5). When interpreted in terms of temporally averaged intensity or total amount of delivered energy, the two pulsed modes required less than one half of the exposure level needed under continuous wave conditions to achieve comparable resorption times. Possibly the attendant, pulsatile agitation of the membrane, clearly visible at 10 Hz prf, causes additional intercellular breakdown that enhances the resorption process.

An alternative mechanism for consideration involves ultrasonically induced streaming in the vitreous that might transport membrane substances to the periphery of the eye and stimulate a general phagocytic response. This seems unlikely because resorption was often observed to be facilitated only within localized membrane segments.

The clinical application of this technique requires precise control of the beam positioning to maximize resorption rate. This requirement is indicated by the variable results seen at lower intensities. In these cases, the disparate rates of resorption within individual membranes apparently resulted because resorption was facilitated most significantly only at those membrane sites intercepted by the beam. In the present experiments, this interception was assessed by visible membrane displacements during insonification. Adjacent sites that resorbed at control rates were probably not intercepted. Thus, accurate beam placement at several sites in the membrane would be required if low-intensity exposures were to produce maximum effects. At high intensities, the need for accurate beam placement seemed less important for causing rapid resorption of the entire membrane. However, accurate beam placement is also required at high intensities if damage to adjacent structures is to be avoided.

The production of chorioretinal lesions emphasizes the need for accurate beam placement. In these animal studies, the chorioretinal lesions seen at high intensities had been anticipated. In the focal plane, the maximum intensities used were much higher (by a factor of about nine) than our previously reported threshold levels for chorioretinal lesions. Thus, even at the periphery of the 3-dB focal volume, these threshold levels could have been exceeded by a factor of more than four. Additionally, the focus was probably frequently situated near the ocular wall in these animal experiments. Membrane resorption rates were significantly increased, however, even when these lesions were not created.

The need for better control of beam position has motivated improvements of the dual transducer system now being used in further experimental investigations. This transducer system is capable of providing accurate beam placement for most efficient placement of the ultrasound energy. Because membranes and ocular walls are visualized, the operator can position the therapeutic focal point so that intensity levels at the retina and choroid do not approach lesion threshold.

As a last consideration, the reported data can be used to form a preliminary assessment of benefit-risk ratios that might be provided by ultrasonic treatment of vitreous membranes. This discussion must, of course, be preliminary because many of the subcategories listed in the Table involve only a few cases, and greater accuracy in beam positioning will most likely improve the benefit accruing from the lower-intensity exposures. However, it is informative to consider the data from this viewpoint that is now being used to select factors for further experiments.

To pursue this topic, benefit and risk are defined in quantitative terms. Benefit is defined as the fractional reduction in resorption time because of the ultrasonic treatment, that is, benefit is equal to $(T - T_u)/T$ where T is the average resorption time of untreated animals (34 days) and T_u is the average resorption time in a category of treated animals. Risk is defined as the ratio of the applied ultrasonic intensity to the threshold intensity required to produce a minimal chorioretinal lesion at the pulse repetition frequency and exposure duration used in treatment. The risk, as defined here, will exceed unity for most reported cases but the control over beam placement can prevent chorioretinal lesions. This definition of risk, however, does serve as a numeric index of potential difficulty in applying this method clinically.

By using these definitions with the data listed in the Table, the risk-benefit implications of various treatment modalities can be compared. A plot of computed benefit vs risk for each of the treatment categories is shown in Figure 5. The computed values have been adjusted so that the maximum benefit and risk are unity. Figure 5 indicates a partitioning of data into quadrants. The first quadrant, containing Categories 6 and 7, provides low risk with low benefit; these treatments involved low intensity, pulsed ultrasound. At the other extreme is the quadrant containing intense continuous wave (Categories 1 and 2). This area yields large benefits but at high risks. The third quadrant contains pulsed Categories 3 to 5, and 8. This region provides the favorable combination of relatively high benefits at low risks. The benefits are comparable to that found for intense continuous wave exposures but the risk is significantly lower.

Figure 5 indicates that certain pulsed applications are most effective from a risk-benefit viewpoint. These are now being explored in more depth. Interpretation of data in terms of risk-benefit considerations is becoming more important in refining this technique because insonification at low pulse repetition frequency values (for example, 1 Hz) lower the in-

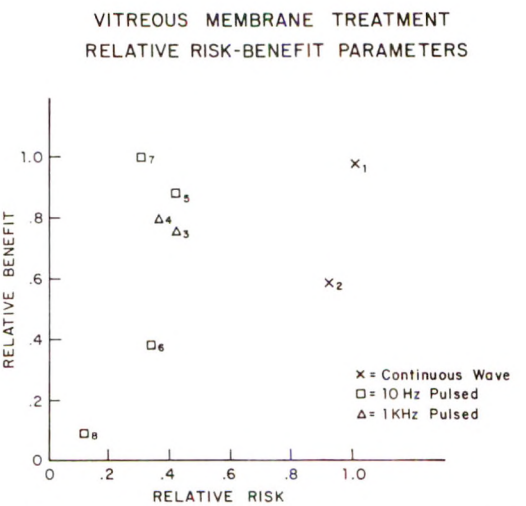

Fig. 5 (Coleman and associates). Benefit vs risk for treatment categories listed in the Table.

tensity threshold for chorioretinal lesions.[17] Thus, comparison of different modalities in terms of only the average intensity does not represent the true risk involved.

Summary

A noninvasive procedure was used to treat membranes within the vitreous with controlled exposure to focused high-intensity ultrasound in rabbit eyes. Membranes were created by injecting small quantities of platelet-rich plasma into the vitreous of the intact globe of anesthetized rabbits. The average time for untreated membranes (controls and shams) to be resorbed was 34 days, whereas the average time to total resorption of membranes treated with ultrasound was 21 days. This comparison showed that high-intensity ultrasound was effective in accelerating the resorption of this type of vitreous membrane. This ultrasound technique is totally noninvasive and can be used without damage to other ocular tissues. Although this animal model departs in some respects from human vitreous membranes, eventual clinical applications are indicated in selected cases where vitrectomy must be delayed or is contraindicated. Noninvasive disruption of vitreous membranes by therapeutic ultrasound offers great promise for reducing the visual limitations produced by such membranes, and eliminating the sequence of disease leading to permanent visual loss.

Acknowledgments

Frederick A. Jakobiec, M.D., and Takeo Iwamoto, M.D., did the light and electron microscopic evaluations. Margaret Cubberly, M.S., prepared the histology specimens.

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AUTOMATED VITRECTOMY IN EYES WITH VITREOCORNEAL TOUCH ASSOCIATED WITH CORNEAL DYSFUNCTION

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Vitreocorneal touch reportedly occurs in 3 to 13% of cases after routine cataract extraction.[1–3] Depending on the cause of vitreocorneal touch, many forms of treatment have been recommended,[4] including the use of miotics, oral glycerin, hypertonic drops, cocaine drops, and supine positioning of the patient. If the vitreous does not retract, an irreversible bullous keratopathy may result, requiring a penetrating keratoplasty.

Recently, several isolated publications have briefly alluded to the therapeutic potential of automated vitrectomy. Peyman and associates[5] reported visual improvement in six of seven patients with vitreocorneal adhesion. Girard, Neives, and Hawkins[6] showed visual improvement in 14 of 18 cases. Young and Shea[7] found visual improvement in two of three eyes treated with automated vitrectomy. These results reflect a subgroup of all patients treated by vitrectomy for various abnormalities. Other than visual acuity, few other objective factors were determined. We evaluated the results of vitrectomy for vitreocorneal touch associated with corneal edema.

SUBJECTS AND METHODS

Seventeen adult patients underwent vitrectomy in one eye for vitreocorneal touch with varying degrees of corneal decompensation. Vitrectomies were done through the pars plana with the Peyman vitrophage (Figure). Care was taken to direct the irrigation port posteriorly to avoid further trauma to the corneal endothelium. Irrigation fluid in all cases consisted of a balanced salt solution containing 4 μg/ml of gentamicin, and glucose. Sodium bicarbonate with and without dextran 40 was also added to the infusion fluid in Cases 1, 3, 5, 8, 12, 14, and 15. All postoperative examinations were performed by one of us (P.I.H.) and compared to preoperative information from the patient's chart, surgical reports, and personal communications with referring physicians. Postoperative evaluation included specular microscopy and fluorescein angiography, whenever possible, to rule out persistent cystoid macular edema. When possible, the specular photo-

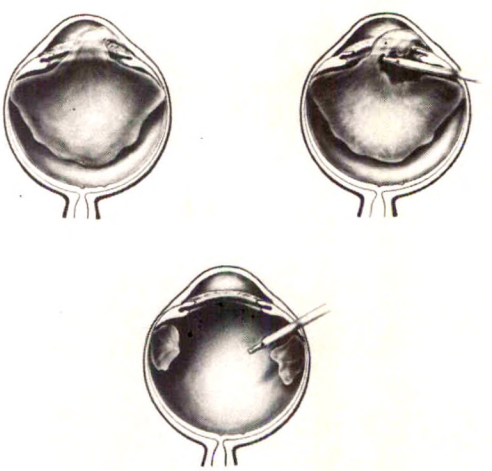

Figure (Homer, Peyman, and Sugar). Left, Schema of vitreocorneal touch. Right, Vitrectomy with the vitrophage. Note that irrigation port is directed away from corneal endothelium. Bottom, Vitrectomy is completed.

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graphic results were based on an average of three frames taken centrally. Additionally, three corneas in our series that were subsequently removed at penetrating keratoplasty because of persistent bullous keratopathy were studied histologically.

Results

No complications at the time of vitrectomy were evident. The vitreocorneal contact was thought to be severed at the time of the procedure in all cases. The vitreous was noted to be unusually thick in five of the 17 cases.

Although there was at least a two-line improvement in the best postoperative visual acuity in 12 of 17 patients, the results in long-term follow-up were not as good. Visual acuity results could be divided into two groups (Table 1). The satisfactory group had a final visual acuity of at least 6/30 (20/100) with stabilization of vision, as defined by one line or better of improvement on the Snellen chart. The unsatisfactory group had final visual acuity of less than 6/30 (20/100).

Some interesting differences and similarities were noted between the two groups. Both groups were homogeneous according to mean age: satisfactory, 68.4

TABLE 1

Results of vitrectomy in vitreocorneal touch*

Case No.	Age (yrs)	Visual Acuity		Follow-up (mos)	Comments
		Preoperative	Postoperative		
			Satisfactory group		
1	63	6/18 (20/60)	6/12 (20/40)	6	Cornea improved; trace epithelial edema
2	79	6/18 (20/60)	6/12 (20/40)	26	Clear cornea
3	66	6/21 (20/70)	6/12 (20/40)	3	Minimal stromal haze
4	68	6/24 (20/80)	6/21 (20/70)	52	Clear cornea; CME†
5	74	6/30 (20/100)	6/12 (20/40)	4	Clear cornea; CME†
6	89	6/60 (20/200)	6/21 (20/70)	42	Senile macular degeneration; band keratopathy
7	63	6/60 (20/200)	6/30 (20/100)	20	Clear cornea; CME†
8	73	6/120 (20/400)	6/9 (20/30)	10	Clear cornea; CME†
9	56	0.6/120 (2/400)	6/7.5 (20/25)	19	Clear cornea; CME
Mean	70.1			20.2	
			Unsatisfactory group		
10	75	6/15 (20/50)	6/120 (20/400)	15	Penetrating keratoplasty
11	81	6/30 (20/100)	LP	33	Uncontrollable glaucoma; epithelial downgrowth; CME
12	67	6/120 (20/400)	6/120 (20/400)	3	Old interstitial keratitis; persistent CME
13	63	6/120 (20/400)	6/120 (20/400)	19	Cornea unchanged
14	64	6/240 (20/800)	CF at 1 meter	12	Penetrating keratoplasty; high intraocular pressure
15	75	1.5/60 (5/200)	6/60 (20/200)	12	Penetrating keratoplasty; CME
16	60	0.3/60 (1/200)	CF at 2 meters	28	Cornea unchanged
17	62	Hand motions	LP	54	Cornea unchanged
Mean	68.4			22.0	

*CME designates cystoid macular edema; LP, light perception; and CF, counting fingers.
†Trace microbullae at 12:00 in Case Nos. 4, 6, and 7.

years; unsatisfactory, 70.1; white to black racial ratio in both groups: satisfactory, 7:2; unsatisfactory, 6:2; sex: satisfactory, 7:2 female to male ratio; unsatisfactory, 7:1; and mean follow-up time: satisfactory, 20.2 months; unsatisfactory, 22.0 months.

Three patients in the satisfactory group and four in the unsatisfactory group had developed vitreous touch within 21 days of initial cataract surgery. The remainder in each group developed vitreous touch more than six months after successful cataract surgery. Vitreous touch and corneal edema were noted at the same time or within one week of each other, possibly because the observer did not look for vitreous touch until corneal edema was noted. Vitreocorneal touch was estimated to cover at least 30% of the posterior cornea in all cases. It was located superocentrally or centrally in all cases.

The satisfactory group was operated on earlier than the unsatisfactory group. Corneal decompensation was noted for 3.6 months (mean) preceding vitrectomy in the satisfactory group vs 16.2 months (mean) in the unsatisfactory group.

The range of preoperative visual acuity was similar in each group: satisfactory, 6/18 (20/60) to 0.6/120 (2/400); unsatisfactory, 6/15 (20/50) to hand motions. However, the unsatisfactory group had more patients with an initial visual acuity ≤ to 6/120 (20/400) (unsatisfactory, 6; satisfactory, 2).

Three of the patients in the unsatisfactory group had an intact hyaloid face touching the cornea. The hyaloid face was thought to be broken in all patients in the satisfactory group.

Early and late complications of cataract surgery were higher in the unsatisfactory group (Table 2). Three of eight patients in the unsatisfactory group had narrowing or closure of the anterior chamber angle as noted by gonioscopy. Vitreous loss at the time of cataract surgery occurred in one patient in the satisfactory group and in two patients in the unsatisfactory group.

TABLE 2

EARLY AND LATE CATARACT SURGERY COMPLICATIONS*

Case No.	Complication
	SATISFACTORY GROUP
1	None
2	None
3	None
4	None
5	None
6	Vitreous loss; previtrectomy IOP = 28 mm Hg
7	CME noted 15 months before vitreous touch appreciated
8	None
9	Iritis
	UNSATISFACTORY GROUP
10	None
11	Pupil block; flat anterior chamber; epithelial downgrowth
12	Retrocorneal membrane
13	Shallow anterior chamber
14	Vitreous loss; unplanned extracapsular extraction; previtrectomy IOP = 38 mm Hg
15	Vitreous loss
16	Hypotony; previtrectomy IOP = 3 mm Hg; shallow anterior chamber
17	None

*CME designates cystoid macular edema.

In both groups a high incidence of bilateral corneal disease was found. One patient had posterior polymorphous dystrophy, one had band keratopathy, and two had fingerprint dystrophy. Eight additional patients showed prominent bilateral cornea guttatae. The patient in Case 12 had old inactive interstitial keratitis in the involved eye. The corneal problems were equally distributed between the two groups.

Ten of 17 corneas showed definite improvement on clinical examination postoperatively, as defined by less bullae or edema, or both. Six corneas showed no worsening; the remaining eye showed

progression of the condition. When improvement was noted, diffuse bullous changes initially resolved centrally. The superior cornea was the last place to clear.

Table 3 shows the results of pachometry in all 17 patients. In the eyes that had preoperative pachometry, seven of nine corneas were less thick after vitrectomy (P = .007; No. = 9). The final mean corneal thickness (0.56 mm) was equal to the contralateral eyes in the satisfactory group. Statistical analysis of pachometry measurements by paired *t*-test revealed the following results (Table 3): For those patients in whom preoperative and postoperative corneal measurements were taken, a statistical improvement was seen in the satisfactory group (P = .003; No. = 5), but not in the unsatisfactory group (P = .39; No. = 4). The difference in postvitrectomy mean corneal thickness between the satisfactory group (.56) and the unsatisfactory group (.65) was statistically significant (P = .011).

TABLE 3

RESULTS OF PACHOMETRY*

Case No.	Preoperative	Postoperative	Contralateral Control
		SATISFACTORY	
1	.72	.62	.60
2	.62	.42	.56
3	.76	.65	Prosthesis
4	—	.60	.48
5	.64	.54	.66
6	—	.64	.61
7	—	.56	.56
8	.76	.56	.56
9	—	.50	.52
Mean	.70	.56	.56
		UNSATISFACTORY	
10	.66	.70	.56
11	—	.60	.56
12	.60	.52	.50
13	—	.74	Prosthesis
14	.72	.64	.67
15	—	.58	.47
16	—	.64	.50
17	.76	.76	.59
Mean	.69	.65	.55

*Corneal thickness (mm).

Specular microscopy was performed on all nine patients in the satisfactory group (Table 4). Cell counts in the operated eye ranged from 329 to a maximum of 1,747/mm^2. In four cases, corneal guttatae were prevalent throughout the central corneal field. This made it impossible to obtain accurate cell counts. The four contralateral unoperated eyes had cell counts ranging from 846 to 1,158/mm^2. This is lower than the range found for an equivalent age group by Bourne and Kaufman[8] (1,600 to 3,000/mm^2).

Fluorescein angiography (Table 5) was performed postoperatively in all patients in the satisfactory group and in three patients in the unsatisfactory group. Bullous keratopathy precluded adequate study in the remainder. Eight of the 12 had unequivocal cystoid macular edema, one had questionable cystoid macular edema, and three had no evidence of it. In most instances postvitrectomy cystoid macular edema correlated with clinical suspicion of it preoperatively. Clinical suspicion of cystoid macular edema was based on either the observation of macular edema or an unexplained poor foveal reflex.

Three of the eyes in the unsatisfactory group required a penetrating keratoplasty (Table 1). The corneal buttons of these eyes were studied histologically. In all cases, endothelium was focally flattened and discontinous, showing a markedly decreased number of endothelial cells. Extensive reduplication of Descemet's membrane was noted in Case 8. A retrocorneal membrane and warts on Descemet's membrane (cornea guttatae) were noted in Case 11. Typical bullous changes were noted in all cases. Vitreous was not adherent to cornea in any of the three specimens.

DISCUSSION

Jaffe[9] believes that once vitreocorneal touch is associated with corneal edema, "relentless progression of corneal edema,

TABLE 4

RESULTS OF SPECULAR MICROSCOPY

Case No.	Endothelial Cell Count: Postvitrectomy (per mm²)	Endothelial Cell Count: Contralateral (per mm²)	Aphakic Contralateral Eye
1	329	846	No
2	Large cornea guttatae	Vitreous touch	Yes
3	Large cornea guttatae, 611	—	Prosthesis
4	1,176	1,568	No
5	Large cornea guttatae	Vitreous touch	Yes
6*	1,747	Vitreous touch	Yes
7	Large cornea guttatae	Large cornea guttatae	No
8	1,372	1,437	No
9	765	1,416	No

*Difficult to get good field secondary to micronystagmus after cerebral vascular accident.

bullous keratopathy, and late opacification" will occur. Our data suggest that early vitrectomy may improve the visual prognosis. This is reflected in the result of patients in the satisfactory group who were operated on a mean of 3.6 months after corneal decompensation as opposed to 16.2 months in the unsatisfactory group. A larger sample size may be needed to see whether this relationship holds true statistically. The number of patients is too small to draw any conclusions regarding the usefulness of the various infusion fluids and their effect on the endothelium. Different infusion fluids are being evaluated presently.

Results from a study using a rabbit model[10] indicate that the solid vitreous component may be more detrimental to the endothelial pump mechanism than liquid vitreous. Because the vitreous face in humans is thought to be a condensation of the solid component, it is not surprising that our three patients with an unbroken face to the cornea did poorly.

The pachometric findings show that

TABLE 5

FLUORESCEIN ANGIOGRAPHIC EVALUATION OF CYSTOID MACULAR EDEMA*

Case No.	Preoperative Suspicion of CME† Clinically	Postoperative Fluorescein Angiogram	Follow-up (mos)
1	No	Negative	2.5
2	No	Negative	27
3	No	Negative	3
4	Yes	Positive	53
5	Yes	Positive	4
6	No	Senile macular degeneration	42
7	Yes	Positive	20
8	Yes	Positive	6
9	Yes	Positive	20
11	Unable to evaluate	Positive	36
12	Unable to evaluate	Positive	3
15	Unable to evaluate	Positive	35
Mean			21.0

*Corneal edema precluded adequate evaluation in the remainder of cases.
†CME designates cystoid macular edema.

there can be improvement in corneal thickness, in selected cases, on removal of vitreous. The final corneal thickness correlates well with satisfactory visual results.

Other factors that correlate well with satisfactory visual results after vitrectomy include the following: (1) early vitrectomy; (2) a previtrectomy visual acuity better than 6/120 (20/400); (3) uncomplicated cataract operation and postoperative course; and (4) a broken rather than an intact hyaloid face.

The results of specular microscopy suggest that there is an extremely wide range of endothelial cell populations compatible with satisfactory corneal function. The cell counts of the unoperated contralateral eyes were lower than one would expect for a similar population.[8]

The high incidence of bilateral corneal abnormalities, as reflected by clinical corneal examination and specular microscopy, shows a compromised corneal endothelium before the onset of vitreous touch. This may be why only certain corneas that sustain vitreous touch develop edema.[1,3]

Additionally, Leahy[1] found that location (3 mm from the corneoscleral limbus) and size of vitreous contact influence the development of corneal edema. Vitreous contact extended at least 3 mm from the corneoscleral limbus in 13 of 17 patients in our series. The estimated size of contact varied between 30 and 60% of the corneal surface in all cases.

Postoperative cystoid macular edema accounted for reduced visual acuity in many of our cases despite clear central corneas. Aphakic cystoid macular edema has been highly correlated with prolapse of vitreous in the past.[11] In 64 eyes with aphakic cystoid macular edema studied by Gass and Norton,[12] 25 eyes had vitreous attachment to the posterior surface of the wound. Cystoid macular edema failed to resolve in five of nine patients in their series who underwent vitrectomy. West, Fitzgerald, and Sewell[13] also found a high incidence of postoperative cystoid macular edema in 15 of 18 patients who underwent penetrating keratoplasty for aphakic bullous keratopathy associated with vitreous touch. It is not surprising, therefore, that eight of 12 of our patients had this problem extending, in many cases, far into the postoperative period. Even in the presence of postoperative cystoid macular edema, there was satisfactory final visual acuity in many of our patients. This may reflect a stabilization or improvement in corneal function after vitrectomy despite the presence of mild cystoid macular edema.

The histologic findings of the three corneas in our series with bullous keratopathy were characteristic of those described for this entity.[14] A retrocorneal membrane found in one of these cases was once thought to be specific for vitreocorneal touch. Recently, this finding has been shown to be present in other forms of aphakic bullous keratopathy.[15]

Our impression is that automated vitrectomy prevents progression of corneal edema and decreasing visual acuity in selected cases. The factors reviewed in this study are currently being evaluated in a prospective study. They include previtrectomy fluorescein angiography, specular microscopy whenever possible, and pachometry.

Summary

Of the results evaluated in 17 patients who had vitrectomy for aphakic vitreocorneal touch associated with corneal edema, nine patients had satisfactory results. Factors associated with a favorable outcome were as follows: (1) early vitrectomy; (2) previtrectomy visual acuity better than 6/120 (20/400); (3) uncomplicated cataract operation and postoperative course; and (4) broken rather than intact hyaloid face. Postoperative cystoid macular edema contributed to decreased visual acuity in eight of 12 patients.

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INTERACTION OF EYELIDS AND TEARS IN CORNEAL WETTING AND THE DYNAMICS OF THE NORMAL HUMAN EYEBLINK

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The maintenance of a clear, healthy cornea requires that the anterior surface of its epithelial layer be kept moist. This is accomplished by the precorneal tear film, which prevents the desiccation of the underlying tissue while providing a smooth, optically refracting interface. Because the tear layer is so thin (typically 6 to 10 μ), evaporation and lipid contamination of the tear fluid's mucin component quickly destroys its continuity. This results in breaks or dry spots that appear, usually within 15 to 30 seconds after a blink, at scattered locations on the corneal surface.[1–3] The blinking action of the eyelids, which usually occurs before the actual formation of dry spots, is required to re-form the tear film layer. This requires that the blink interval be shorter than the film break-up time.

In a properly functioning eyelid-tear system, corneal wetting is both efficient and automatic. Recently, the complexity of the process of eyelid blink and tear film formation has been recognized, as has the structural nature of the tear film layer itself.[4,5] The treatment of many dry-eye disorders, such as exposure keratitis, keratitis sicca, and Sjögren's syndrome, usually involves eyelid and tear film considerations, particularly the spreading of the tear fluid by the blinking action of the eyelids. The objective of this study was a comprehensive examination of the dynamics of eyelid motion during blinking in normal subjects and its implications of interaction between blinking and corneal wetting. This will provide a baseline with which various dry-eye conditions can be compared.

Studies of corneal wetting have dealt with the more or less static characteristics of the tear film. Although the tear film is easily accessible, its fleeting, dynamic nature poses difficulties in determining exactly what takes place during the rapid motion of the blinking eyelids. In the few studies using photography, the inadequate rate at which pictures were taken prevented detailed measurements of eyelid dynamics. The present study shows that typical eyelid closure occurs in about 80 msec. Even at 64 frames/sec (four times normal silent film rate), the entire downward motion of the upper eyelid is represented by at most four frames. This is not rapid enough for detailed temporal resolution of eyelid motion.

An additional difficulty with previous studies was the subject's awareness that photography was being done.[6,7] This, and the experimental lighting levels and eyelid manipulation used, raise doubts about whether natural eyelid dynamics, that is, normal, unforced blink action, were being recorded. The study reported here was designed to circumvent such problems.

SUBJECTS AND METHODS

Subjects—The subjects were between 20 and 50 years of age, with no ocular problems except for a few instances of mild myopia or hyperopia. More than 25 subjects were filmed; in ten of these, detailed analysis of eyelid motion was

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made. All subjects were used for general determinations of blink completeness, and globe and eyelid motion characteristics. Frequency of blinking is known to be greatly affected by many external factors, and was not a part of the study, which mainly concerned the recording of high-speed events.

Instrumentation—Detailed photographic analysis of eyelid motion during blinking was accomplished with a Redlake 16-mm high-speed motion picture camera. This device allows filming rates of 16 to 500 frames/sec. An intermittent, pin-registered type of film transport ensures that each film frame is stationary during its exposure period, regardless of speed. A dual timing light, with its associated timebase generator, was incorporated in the camera. This enabled a photo-emitting diode to flash at a precise rate of 100/sec when the film was moving, resulting in timing marks on the edges of the film during exposure. This allowed accurate time measurements to be correlated with the recorded events. A reflex tracking viewfinder with a prism beamsplitter was attached to the camera, providing real time viewing of the subject through the camera's optics during the filming. Magnification was calibrated by photographing a millimeter scale under the identical conditions of data acquisition. The measurement of this scale in the resultant projected image provided accurate magnification information for eyelid excursion and velocity determinations.

Camera setups—Eyelid motion data were acquired with two different camera setups. In one setup, the subject was unaware that his blinks were being photographed. It is important to record natural, nonconscious blinking, particularly when the overall characteristics of the eyelid motion are to be determined. In practice, this presents some difficulty, because the filming procedure itself is hardly inconspicuous. To this end, a special filming site was constructed, with the subject located in one room and the camera system in an adjacent room. A specially made one-way glass mirror, 20 cm^2 and transmitting 40% light, was incorporated into the wall separating the two rooms. The subject sat facing this wall, 3 meters distant, with head positioned by a modified slit-lamp stand. The subject looked directly into the one-way glass, which was tilted slightly backward, and saw a reversed Snellen-type visual acuity chart located on the wall above and behind him. Thus, at the same time, the subject also looked directly into the camera system located on the other side of the wall (Fig. 1).

Two fiberoptic illuminators with associated fiber bundles were mounted on the slit-lamp stand and directed illumination toward the subject's eye, usually at an oblique angle to avoid tear stimulation and uncomfortable brightness. When fluorescein was used, appropriate filters were incorporated in the illuminators.

The camera system in this remote situation was almost 4 meters from the subject, necessitating the use of a long-focus lens. A 600-mm f/4.5 lens, designed by Canon for 35-mm format coverage, was adapted for use with the Redlake camera. A long extension tube was required to enable the lens to focus at the relatively close (for such a long telephoto lens) distances involved. Use of this system allowed filling the 16-mm film frame with the image of one eye from a distance of 4 meters from the subject.

The camera and lens system required a stable mounting base. The camera itself was mounted on a large lens cradle, which also supported the front portion of the lens. This cradle, in turn, was fastened to a tiltable mount, capable of rotation in both the vertical and horizontal planes. The cradle, camera, and tilting mount were fastened to a large, heavy, double-translation stage, providing rack-and-pinion motion both side-to-side and front-to-back over an 8-cm range. The entire setup rested on a 600-lb marble instrument table (Fig. 2).

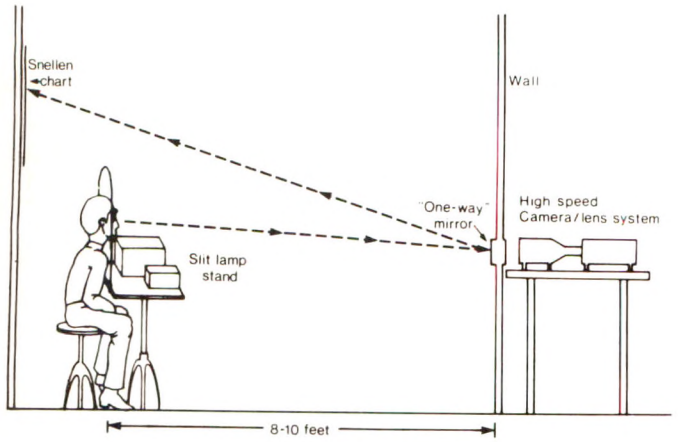

Fig. 1 (Doane). Filming site for unobserved photography. The subject views a Snellen visual acuity chart by looking into a one-way mirror. The camera is located in an adjacent room directly behind the mirror.

When this system was used for unobserved photography, the subjects were initially told that their visual acuity was going to be measured, and visual acuity changes noted after light was made obliquely incident upon their eye, that is, glare effect. The illuminating sources were turned on and the subjects were told to relax and let their eyes become adapted to the light. Often during this time the subjects were simply ignored for several minutes. Toward the end of this relaxation period, the filming was actually accomplished; it lasted from eight to 45 seconds, depending on the film framing rate used. This filming was done before the subjects were told to read the chart and no specific instructions were given before filming. The number of blinks photographed varied, because the subjects were not told to blink, merely to relax.

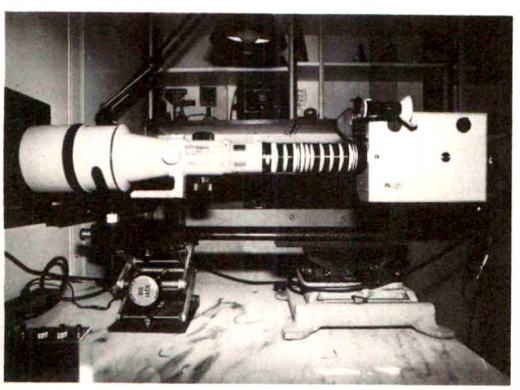

Fig. 2 (Doane). High-speed camera and telephoto lens system.

The second filming setup was simpler. The camera was near the subject, who was aware of the photography. Normal close-up techniques were used, usually with a Nikon 200-mm lens, with custom-made adapters to allow the use of special close-up auxiliary lenses. The simpler filming situation yielded better image quality, and was used for detailed recording of globe retraction and tear film details, with the understanding that some forced blinking would occur.

Lighting—One severe problem in photography as described previously is light levels. The shutter of the Redlake camera is adjustable to allow for variation in effective shutter speeds (or, more directly, exposure time per frame). In general, the shutter was set for effective exposure times of one-third the frame rate. Thus, at 500 frames/sec, the effective exposure time was 1/1,500 sec. This short time, plus the light loss from the beamsplitting viewfinder, the small effective aperture of the lens system, and the 60% light loss through the one-way mirror, all exacerbate the lighting problem. Additionally, excessive light intensity on the subject's eye would stimulate tearing, which is undesirable. To allow use of acceptable light levels, highly sensitive film was used. Usually, when maximum light sensitivity was required, a black and white

surveillance film, Kodak 2475, was used. This was push-processed in Kodak DK-50 developer, raising its effective ASA exposure index from 1,000 to near 4,000. Although the resulting negatives had high contrast and coarse grain, the resolution was sufficient for eyelid motion dynamics to be accurately determined. If more light was needed, or longer exposure times were acceptable, these were obtained by using a somewhat slower framing rate or by using the close-up position; then a color reversal film, Eastman Ektachrome Video News Film, High Speed 7250, Tungsten, was used. This was push-processed from its normal ASA exposure index of 400 to 1,600 or above.

Film analysis and data acquisition and treatment—Detailed analysis of the film was accomplished with either a Lafayette AA-300 motion analysis projector or a DF-16B Dynamic Frame stop-motion analysis projector. Both machines allow projection running speeds of one to 24 frames/sec, as well as single frame advance and reverse. Wide-aperture film gates allowed the timing reference marks along the film margin to be projected with each frame. By using frame-by-frame projection onto large sheets of gridded paper (overall magnification, ×22), drawings of sequential eyelid positions were made, which allowed accurate determination of eyelid velocity and configuration changes, as well as of globe movements. At 500 frames/sec, the positional changes in the eyelids can be seen for each 2 msec of elapsed time. Both profile and straight-ahead filming was done.

The data on eyelid displacement vs time was tabulated and then entered into a computer for processing. The computer was programmed to divide the total data-gathering time period (blink time, about 1/3 sec) into many time windows, taking the data points within each window and calculating the curve of a cubic parabola on a best-fit basis. Starting at the beginning of the blink data, the window then slid forward one data point at a time, calculating a new curve to fit the data within each successive window, until all the data were represented by the curve. The net result was similar to a French-curve fit to the data, both for displacement vs time and for velocity vs time. The time width of the sampling window could be varied; obviously, the wider the window, the smoother the curve, but also the greater the loss of short-term-variation information. In practice, a window width of 1/20 of the total data sampling period (about 16 msec) offered the best compromise between smoothing and preservation of details of the short-term variations.

Several hundred blinks were recorded on over 10,000 feet of film. More than 60 blinks have been analyzed in detail, frame-by-frame; the remainder have been examined for such general characteristics as overall eyelid motion, completeness of closure, globe movement, and tearing factors.

Results

The upper eyelid accelerates rapidly as it descends, and reaches its maximum speed by the time it crosses the visual axis. It then begins to decelerate, often coming to rest before making contact with the lower eyelid. Most blinks in most subjects were not complete. In a few instances, a complete blink was never observed during a filming period with the hidden camera (typically eight to 45 seconds of filming time per session, depending upon film framing rate).

Examples of upper eyelid displacement and velocity vs time during several successive blinks in four subjects are shown in Figure 3. The lowest point of the upper curve represents the farthest eyelid displacement, that is, the most closed position. After a brief time in which the eyelid is stationary, in the closed phase of the blink, the eyelid rapidly accelerates as it

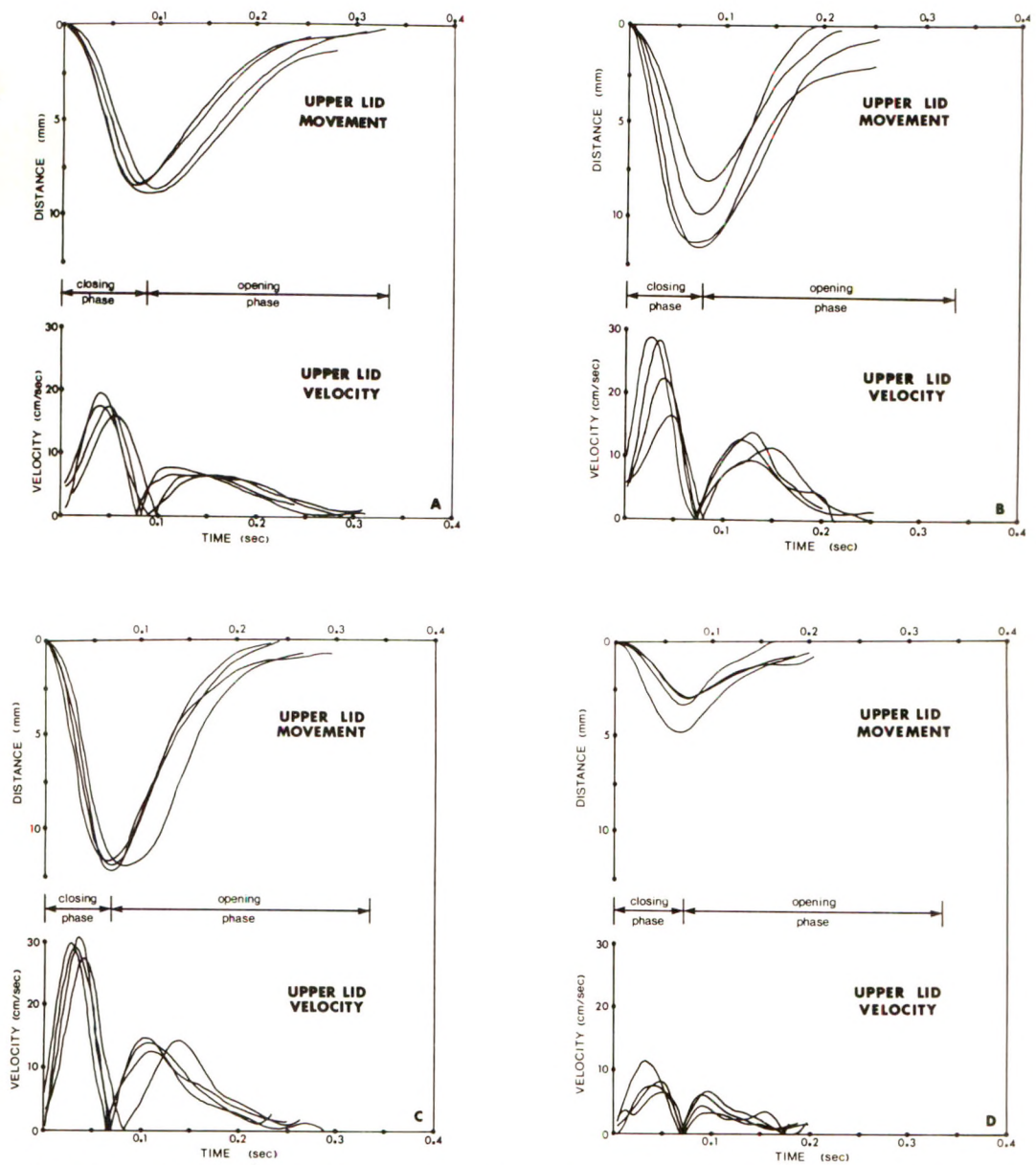

Fig. 3 (Doane). Displacement and velocity characteristics of upper eyelid movement in four subjects. The curves for each subject represent four consecutive blinks. The upper curves of each set represent the excursion of the eyelid; the lower curves, the computer-generated instantaneous velocities of the eyelid during its closing and opening phases, on the same time base.

moves upward toward its starting position. This opening motion slows significantly as the eyelid rises, the last few millimeters of movement being accomplished at a relatively slow rate. The steeper the displacement curve, the greater the acceleration. The lower curve of each pair is the mathematical derivative of the displacement curve, derived by the computer processing, and represents the instantaneous velocity of the upper eyelid as a function of time from the start of the blink.

There were considerable variations in eyelid dynamics between individuals; the factors from blink to blink in the same subject were more consistent. This was true even when data were compared from several filming periods for the subject during more than a year's time. The characteristics that showed the greatest variation between individuals were the peak velocity of the descending upper eyelid and the total extent of travel of both eyelids.

In the examples shown in Figure 3, upper eyelid maximum excursion ranges from 5 to 13 mm, and peak velocities from 8 to 30 cm/sec. The low values for subject D (Fig. 3, bottom right) are unusual; this individual had a narrow palpebral fissure and all blinks were incomplete. Subject A (Fig. 3, top left) is perhaps the most typical example, with upper eyelid excursions of 8 to 9 mm and velocities of 16 to 19 cm/sec. In every instance in all subjects, the opening (ascending) upper eyelid traveled much more slowly than it did when closing.

The movement of the upper eyelid is rapid as it crosses the visual axis; the velocity is usually 15 to 25 cm/sec, but a few instances over 40 cm/sec were noted. Over 50 films taken from the hidden camera location show that during normal, nonconscious blinks, with the subject free to fixate on any object, most blinks are incomplete, with the eyelids not touching.

Because of the great variation in eyelid motion characteristics between individuals, including the degree of completeness of blinks, a typical time profile may be different from any specific example. For convenience, however, the values in the Table may be considered representative of a standard fast blink. The stationary phase between the closing and the opening of the eyelids during a normal, nonconscious blink is short, on the order of 3 to 5 msec. Because the best time resolution obtainable at the fastest speed of 500 frames/sec is 2 msec, clear distinctions between the exact start and end of such short events were not possible. Voluntary, conscious blinks will nearly always be of longer duration than nonconscious blinks, because the former are more complete, with larger excursions. Also, such forced, conscious blinks have a much longer stationary period between the closing and opening phases, often approaching 30 msec in duration.

The primary motion of the lower eyelid during a blink is a horizontal translation in a nasal direction, sometimes accompanied by a downward movement of 1 or 2 mm. Total lateral movement is about 2 to 5 mm, with the motion synchronized with the upper eyelid's descent (Fig. 4). When there is complete eyelid closure and contact, the nasally directed translation of the lower eyelid will carry the upper eyelid along with it. The start of the opening phase is seen as the beginning of

TABLE

DYNAMICS OF UPPER EYELID MOTION DURING A BLINK*

Factor	Value
Duration of closing phase	82.1 ± 2.1 msec
Duration of opening phase	175.8 ± 11.0 msec
Total blink duration	257.9 ± 11.3 msec
Maximum closing velocity	18.7 ± 1.7 cm/sec
Maximum opening velocity	9.7 ± 0.7 cm/sec

*Each value is an average of 40 blinks, ± standard error of the mean, in ten different subjects.

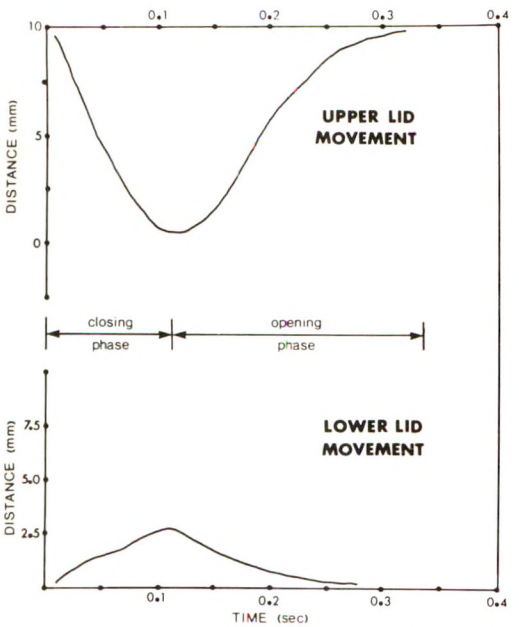

Fig. 4 (Doane). Upper eyelid motion (down, then up) and lower eyelid motion (nasal, then temporal) for the same blink.

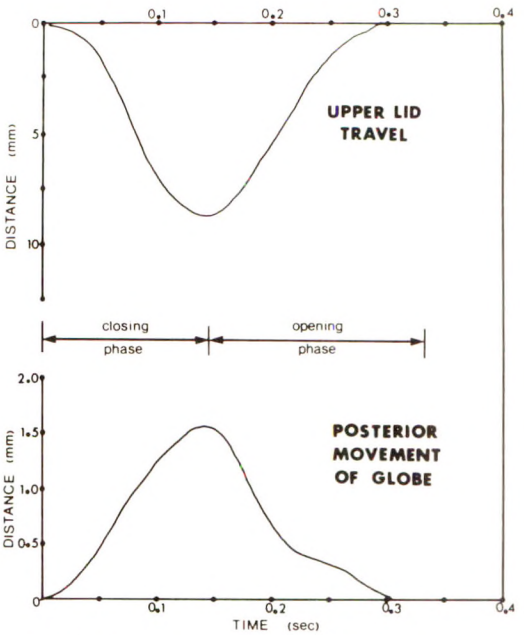

Fig. 5 (Doane). Upper eyelid motion and posterior movement of the globe, for the same blink. Note that the vertical scales, representing displacement distance, differ for the two movements.

motion of the lower eyelid in a temporal direction toward its resting, central position. Frequently, the return of the lower eyelid starts several hundredths of a second before the upper eyelid begins its opening, upward motion.

There is little tendency for Bell's phenomenon in normal, fast blinks. In most instances, there is no significant upward rotation of the globe during the blink, unless the eyelid is restrained or the blink is strong and forced. This finding is somewhat contrary to what many have come to believe, that is, that Bell's motion occurs during most blinks.

Although the globe does not normally rotate upward during blinking, it does move in a posterior-anterior direction. This implies that there is considerable pressure exerted on the anterior surface of the globe by the descending upper eyelid. There is good correlation between the descent of the eyelid and the retraction of the globe (Fig. 5). Both upper eyelid movement and globe retraction are shown for the same blink, on the same time scale. The amount of posterior movement of the globe varies considerably between individuals, ranging between 0.7 and 1.6 mm, perhaps reflecting differences in eyelid tightness. Examples of posterior movement of the globe during several successive blinks are shown in Figure 6. The data for globe retraction were obtained with the camera axis perpendicular to the direction of gaze of the subject.

The eyelids are efficient in mixing the tear fluid and spreading it over the corneal surface. A 1-μl drop of concentrated fluorescein solution, carefully applied to the temporal corner of the eyelid junction, is well mixed after only one blink of the eyelids. The applied drop first runs along the lower tear meniscus at the upper edge of the lower eyelid. With a complete blink, the upper eyelid then touches this strip of solution, and as it opens, it carries the fluorescein over virtually the entire exposed surface of the globe. With a

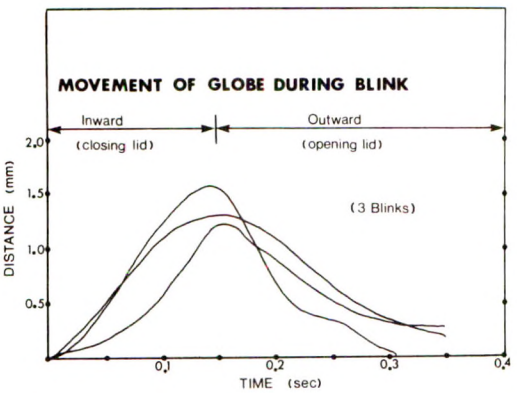

Fig. 6 (Doane). Posterior-anterior movement of the globe for three successive blinks in the same subject. Globe retraction ranged from 1.3 to 1.6 mm in these cases.

microdrop of solution much less than 1 μl, several blinks of the eyelid usually are required for a fairly uniform distribution of the dye.

Discussion

Eyelid motion, globe movement, tear distribution, and tear drainage are all intimately related in serving the crucial function of maintaining a clean, stable tear film layer over the corneal surface. The date on eyelid and globe motion reported here are part of a comprehensive study; data on tear mixing and drainage will be presented in more detail later.

Because most normal, nonconscious blinks are incomplete, an area of the inferior cornea is not wiped and wetted as frequently as the remainder of the corneal surface. There appeared to be no deleterious effects, indicating that the truly complete blinks occurred frequently enough to prevent problems.

Incomplete blinks are faster (that is, last a shorter time from start to finish) than complete blinks, because the eyelids do not move as far and because the time that the eyelids are stationary is shorter. Thus, because incomplete blinks seem to appear frequently during times when the subject is fixating his gaze, vision is obscured for a shorter time than if the blink were complete. This may be the reason for such a high frequency of incomplete blinks. It is well known, for instance, that such visual tasks as reading tend to be accompanied by less frequent blinking, again indicating a minimization of the time that vision is obscured. In any case, the percentage of incomplete blinks that occur under such circumstances is much higher than previously reported. Results of earlier blink studies have been skewed because they reported voluntary, conscious blinks, which are nearly always complete.

It is the downward motion of the upper eyelid that wipes the cornea clear of any accumulated debris, and a few blinks will usually carry such material into the lower tear meniscus where it remains when the eyelid rises. Then, the nasally directed horizontal movement of the lower eyelid during the next few blinks moves the debris toward the medial canthus. Once there, it will either exit via the punctal-canaliculi drainage system, or collect in the region of the eyelid junction, where it can be removed by a swipe of a finger. The horizontal translation of the lower eyelid appears to play a primary role in the normal tear turnover process. In many individuals, the lower eyelid also moves downward 1 or 2 mm during the descent of the upper eyelid, giving the subjective impression that the globe is rotating upward.

The importance of distinguishing between nonconscious, natural blinks and those of a voluntary nature must be emphasized. Not only are the time factors changed, but the percentage of complete blinks is different. In a given subject, 75% or more of the blinks may be incomplete when the photography is done through the one-way mirror and the subject is unaware that blinking is the topic of interest. The same individual will typi-

cally show all, or nearly all, blinks to be complete when the subject knows that the blinking process is being photographed. This is the case despite explicit instructions for the subject to blink naturally and not to force eyelid closure. Evidently, to the subject, a normal blink is a complete eyelid closure.

The measurable retraction (or pushing inward) of the globe during the descent of the upper eyelid might have been anticipated. There have been several reports of measurements of considerable force exerted by the eyelid as closure is accomplished. For instance, Burton [8] found that the upper eyelid exerts a squeeze force of 50 to 70 g. Miller[9] reported that the average pressure developed during a blink was 10.3 mm Hg. Such pressure would ensure intimate contact between the inner surface of the upper eyelid and the cornea. Studies by Holly[10] and Holly and Lemp[11] showed that it is important that the wiping action of the upper eyelid clean off the mucin layer of the tear film adjacent to the corneal epithelium. A short time after the re-forming of the tear film by the blink action, this mucin layer is thought to become contaminated by the overlying lipid layer, impairing the wetting ability of the mucin. The mucin, which is the natural detergent of the tear fluid, can then no longer aid in the wetting ability of the epithelium (normally hydrophobic), and dry spots will form. Thus, the close contact of the eyelid with the cornea aids in replacing this mucin on a periodic basis, perhaps actually rubbing fresh mucin onto the corneal surface. The posterior movement of the globe during the blink supports the concept that the eyelid pressure must be significant, and is an important factor in the corneal wetting mechanism.

It is commonly but incorrectly believed that the upward rotation of the globe associated with Bell's phenomenon occurs during normal blinking. The confusion arises because of the difference between normal, unforced blinks and those that are voluntary or where the eyelid is restrained from its normal motion. Upward rotation of some 15 degrees during a normal blink, and even more during a protective reflex blink, have been reported.[12] Such large excursions occur only in cases of a strong, forced blink, or when the eyelid is held or restrained. In the many films examined in this study, the amount of upward rotation seems to be generally correlated with the effort involved in the blink. Duke-Elder and Scott's[13] statement that "in voluntary closure, it (upward rotation) varies in extent directly with the amount of energy expended in the act of closure, being absent when little effort is involved," is confirmed by the high-speed photography. Little effort is involved in normal, nonconscious blinking, and Bell's phenomenon does not normally occur in most blinks.

There is a tendency toward upward globe rotation when there is discomfort upon blinking, as when debris is on the eye or when a contact lens is uncomfortable. Photography of two subjects who had worn hard contact lenses for more than ten years with no discomfort showed no Bell's motion during normal blinking. The limits of detectable movement with the projection system were approximately 0.1 mm, or one-half degree of arc, so that rotations below this magnitude are not considered here. Certainly such small displacements would be unimportant in corneal wetting.

Summary

We used a high-speed camera system to study in detail the eyelid motion dynamics of the human eyeblink. Films were made from a hidden location through a one-way mirror. In this manner, normal, unforced blinks were recorded.

The descent of the upper eyelid

reached its maximum speed at about the time that it crossed the visual axis, generally in the range of 17 to 20 cm/sec, but occasionally reaching a speed of over 40 cm/sec. The motion of the lower eyelid was mostly horizontal, in a nasally directed movement, with a total displacement in the range of 2 to 5 mm.

A distinction must be made between normal, unforced blinks, and voluntary, forced eyelid motion. In a normal blink, no appreciable upward rotation of the globe is observed. A forced blink or a restraint of motion of the upper eyelid results in a significant demonstration of Bell's movement. The globe moves posteriorly up to 1 to 6 mm as the upper eyelid descends, probably caused by eyelid pressure during the closing phase of the blink.

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LOWER EYELID RETRACTION AFTER BLEPHAROPLASTY

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Retraction of the lower eyelid is a potential complication of blepharoplasty or of other surgical procedures that use a blepharoplasty eyelid incision.

The basic mechanism in postoperative lower eyelid retraction is scarring and contraction of tissues in the plane of the orbital septum or an actual vertical shortening of the orbital septum (Fig. 1). The orbital septum may be shortened if it is inadvertently dissected with a skin-muscle flap, if it is sutured after removal of orbital fat, or if the lower eyelid is held in a downward position after lower eyelid surgery. The lower eyelid retractors and the skin are not involved in cases of pure retraction of the eyelid. When firm upward traction is applied to the retracted lower eyelid, no shortage of skin is manifest and no elevation of the eye is noted (Fig. 2).

Smith and Edgerton[1,2] discussed the treatment of vertical shortening of the lower eyelid after blepharoplasty. Smith[1] described the use of radiation for hypertrophic scarring, surgery, and grafting. Edgerton[2] described release and mobilization of the eyelid by incision of the orbital septum and a Frost suture to maintain elevation of the eyelid.

Lower eyelid retraction noted in the immediate postoperative period has been successfully treated in one patient (one eyelid) by simply applying firm upward traction on the lower eyelid.

Long-standing postoperative lower eyelid retraction has been successfully treated according to the basic principles outlined by Edgerton,[2] but using a relatively small skin incision and a precise means of maintaining elevation of the mobilized lower eyelid. We describe a simple effective procedure for correcting this lower eyelid retraction.

Fig. 1 (Hamako and Baylis). Left, Normal inferior orbital septum. Right, Shortened inferior orbital septum with lower eyelid retraction.

MATERIAL AND METHODS

Anesthesia may be general, or it may be local in a cooperative patient. A lateral canthotomy is performed exposing the

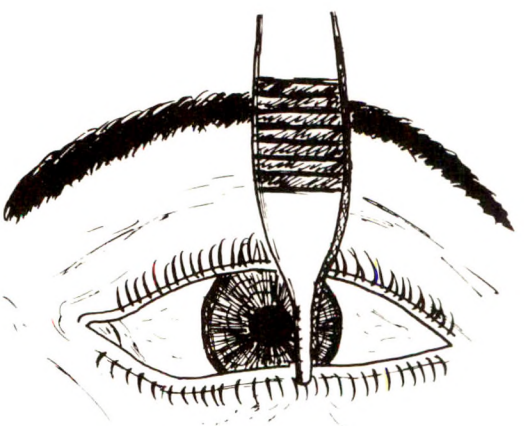

Fig. 2 (Hamako and Baylis). Fixation of the retracted lower eyelid without evidence of shortage of skin and without elevation of the eye.

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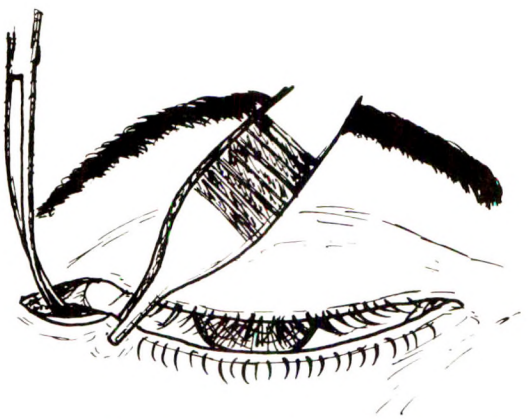

Fig. 3 (Hamako and Baylis). Lower limb of the lateral canthal tendon lysed at the orbital rim.

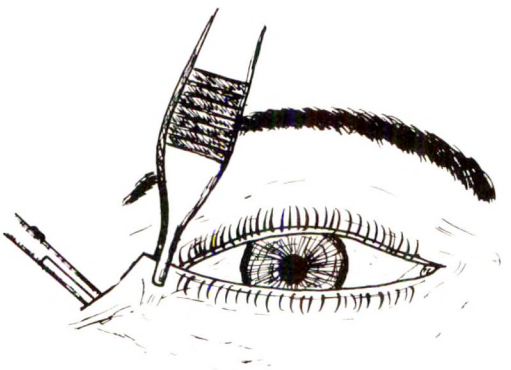

Fig. 4 (Hamako and Baylis). Retracting layer of tissue within the lower eyelid palpated and lysed close to the inferior orbital rim.

lateral orbital rim and the lateral canthal tendon. The skin and orbicularis incision is extended to the posterior aspect of the lateral orbital rim. The lower limb of the lateral canthal tendon is lysed with scissors at the orbital rim (Fig. 3). The skin of the lower eyelid is undermined with scissors through the lateral canthotomy skin incision. The retracting tissue layer within the lower eyelid is palpated with scissors and lysed close to the inferior orbital rim, as far nasally as required to allow mobilization of the lower eyelid (Fig. 4). When the retraction is adequately relieved, the lower eyelid may be freely drawn upward (Fig. 5). A tongue of lateral canthal tendon and lateral tarsus with overlying orbicularis muscle is fashioned in the following manner as previously described by Tenzel.[3] The lower eyelid is drawn up into the desired position, the location of the new lateral canthal angle is identified along the lower eyelid and the eyelid margin is excised from the overlapping lateral segment of the lower eyelid (Fig. 6, left). The skin is reflected forward to the point along the lower eyelid margin where the new lateral canthal angle has been localized (Fig. 6, right). The conjunctiva on the posterior aspect of this

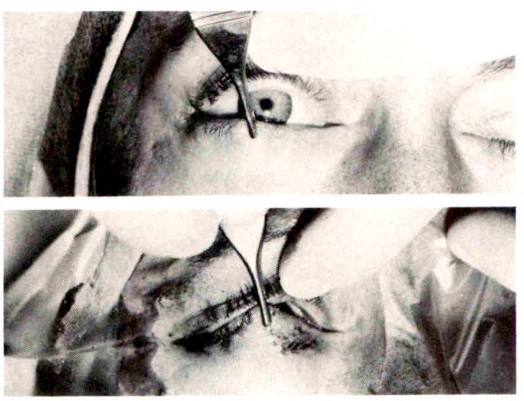

Fig. 5 (Hamako and Baylis). Top, Fixation of the retracted lower eyelid postoperatively. Bottom, Free upward movement of the mobilized lower eyelid after lysis of the retracting layer of tissue.

Fig. 6 (Hamako and Baylis). Left, Desired position of the new lateral canthal angle determined along the lower eyelid margin. Right, Eyelid margin excised from the overlapping lateral segment of the eyelid and skin reflected forward. Tongue of lateral canthal tendon and lateral tarsus exposed. Desired position of the lower eyelid and lateral eyelid tongue.

tongue is dissected free from the overlying eyelid retractors and tarsus. The conjunctiva firmly adherent to the upper aspect of the tarsus is vigorously scraped with a knife blade to remove the epithelium. The orbital rim is exposed and a posteriorly based periosteal flap is outlined with a knife blade. This periosteal flap is raised with a periosteal elevator. The location of this flap, above the lateral canthal angle, is identified by drawing the lateral aspect of the lower eyelid upward into a slightly overcorrected position. Each arm of a double-armed 4-0 black silk suture is passed through the lateral tongue of the lower eyelid from the anterior to the posterior surface (Fig. 7, left). Each arm of the silk suture is then passed under the periosteal flap and through its base (Fig. 7, right). The eyelid tongue is drawn into position under the periosteal flap. Each arm of the silk suture is passed upward under the orbicularis muscle, close to the periosteum, and out to the skin surface at the lateral aspect of the eyebrow (Fig. 8, left). The silk suture is tied over a cotton bolster and interrupted 5-0 Dexon sutures are used to secure the periosteal flap and eyelid tongue to the edges of the intact periosteum (Fig. 8, right). The skin incision may be left unsutured or it may be closed loosely with interrupted sutures (Fig. 9). A combination antibiotic and corticosteroid ointment is applied to the lower conjunctival cul-de-sac and to the skin incision. A firm dressing is placed over the lateral canthal area and allowed to remain in place for 12 to 24 hours. Skin sutures, if present, may be removed in three to five days. The 4-0 silk suture is removed in ten to 14 days.

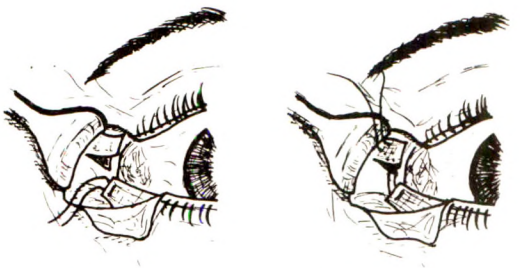

Fig. 7 (Hamako and Baylis). Left, Double armed 4-0 black silk suture placed through the eyelid tongue. Right, Silk suture passed through the base of the periosteal flap.

Results

We have used this procedure with excellent results in seven lower eyelids of five patients. Four patients (six eyelids) required corrective surgery for retraction that occurred after blepharoplasty. One patient (one eyelid) required corrective surgery for retraction that occurred after repair of an orbital floor fracture.

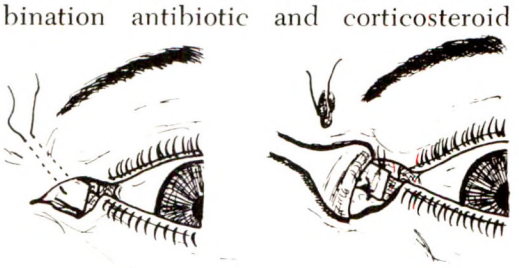

Fig. 8 (Hamako and Baylis). Left, Silk suture passed upward under the orbicularis muscle and out to the skin surface at the lateral aspect of the brow. Right, Silk suture tied over a cotton bolster and interrupted 5-0 Dexon sutures securing the periosteal flap and eyelid tongue to the edges of intact periosteum.

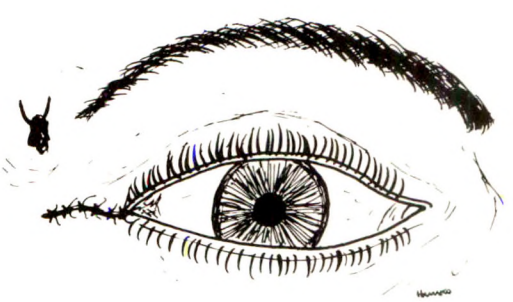

Fig. 9 (Hamako and Baylis). Interrupted sutures used to close the lateral canthal skin incision. Lower eyelid in a slightly overcorrected position.

No problem with eyelid-to-globe apposition has occurred in the lateral canthal area after this procedure. No significant shortening of the horizontal dimension of the palpebral fissure has been noted after this procedure. Postoperative drooping of the lower eyelid has not occurred in this series of patients; however, in one instance a lower eyelid suspended by the described technique for lagophthalmos did develop recurrent postoperative lagophthalmos.

Case Reports

Case 1—A 35-year-old man had retraction of the right lower eyelid after repair of an orbital floor fracture through a subciliary skin incision with a skin-muscle flap (Fig. 10, top). Upward traction on the lower eyelids shows fixation of the right lower eyelid in a retracted position (Fig. 10, bottom).

Case 2—A 34-year-old woman had retraction of both lower eyelids after skin-muscle flap blepharoplasty (Fig. 11, top). The retraction did not resolve with time or with conservative measures. Corrective surgery was performed on both lower eyelids and an excellent result was achieved (Fig. 11, bottom). The patient continues to have excellent eyelid position more than two years after surgery.

Case 3—A 32-year-old woman had retraction of both lower eyelids after multiple lower eyelid blepharoplasties. Retraction of the right lower eyelid was worse than the left lower eyelid (Fig. 12, top). Corrective surgery was performed on the right lower eyelid and an excellent result was achieved (Fig. 12, bottom). The patient continues to have excellent eyelid position more than two years after surgery.

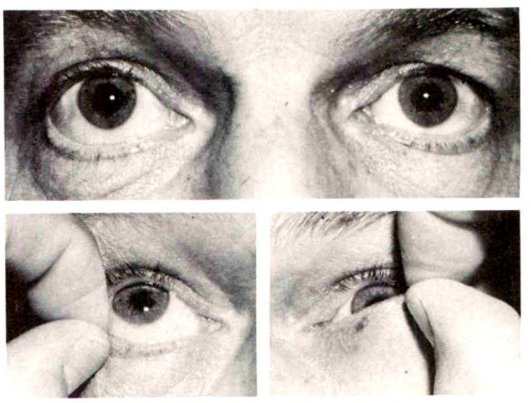

Fig. 10 (Hamako and Baylis). Top, Right lower eyelid retraction after subciliary skin approach orbital floor repair. Bottom, Fixation of the retracted right lower eyelid.

Discussion

Lower eyelid retraction is not discussed often as a potential complication of blepharoplasty even though it may be as common as, or possibly more common than, postoperative lower eyelid ectropion. Lower eyelid retraction is probably less often discussed because it may be a minimal defect that is not as noticeable and not as objectionable as ectropion. Also, lower eyelid retraction, unless severe, may not be considered for corrective surgery. However, an attempt usually would be

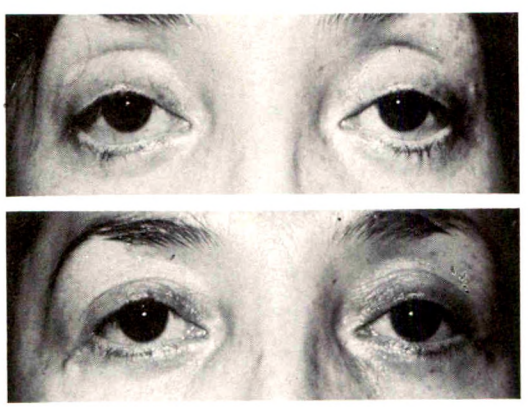

Fig. 11 (Hamako and Baylis). Top, Retraction of both lower eyelids after blepharoplasty. Bottom, Lower eyelid position five months after corrective surgery.

Fig. 12 (Hamako and Baylis). Top, Retraction of the right lower eyelid after blepharoplasty. Bottom, Lower eyelid position four weeks after corrective surgery.

made to correct even a slight degree of ectropion.

All five patients undergoing corrective surgery for postoperative lower eyelid retraction in this series had the primary complaint relating to cosmesis. Ocular irritation was the original complaint of one patient not included in the series. This patient was noted to have minimal bilateral lower eyelid retraction after blepharoplasty. This patient elected not to have corrective surgery even though the symptoms were relieved by elevating the lower eyelids temporarily with tape.

Prevention of postoperative lower eyelid retraction might be accomplished by applying upward pressure on the lower eyelid with a compress or a dressing immediately after surgery. A Frost suture might also be used to apply upward traction on the lower eyelid postoperatively. One of us (H.I.B.) has corrected post-blepharoplasty retraction of one lower eyelid during the early postoperative period (third day) by simply applying firm upward traction on the eyelid.

Lower eyelid retraction identified in the late postoperative period may respond to vigorous massage; however, we have not had success with such treatment. All of the patients in this series were referred for evaluation only after conservative forms of treatment, such as eyelid massage, had failed.

Grafting procedures, although more complicated, may be equally successful in correcting postoperative lower eyelid retraction. Sclera or tarsus placed between the inferior tarsal border and the superior margin of the retracting tissue layer may be used to increase the vertical height of a retracted lower eyelid. A skin graft may be necessary in conjunction with a scleral or a tarsal graft if the vertical height of the eyelid must be expanded beyond the limit of the existing skin. A skin graft alone will not relieve retraction of the lower eyelid that occurs at the level of the orbital septum.

Although we have encountered no complications with the reported procedure, blind release of the orbital septum from the inferior orbital rim could potentially cause orbital hemorrhage and loss of vision. Release of the orbital septum and the retracting tissue layer under direct visualization with a blepharoplasty skin flap might decrease the possibility of this potential complication.

Summary

We used a simple procedure to correct retraction of the lower eyelid after blepharoplasty. Through a lateral canthotomy skin incision, the retracting layer of tissue within the lower eyelid at the level of the orbital septum is lysed and the lower eyelid is mobilized. The level of the lower eyelid is elevated and fixed in the desired position by attaching a tongue of lateral canthal tendon and lateral tarsus to the lateral orbital rim under a posteriorly based periosteal flap.

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CONGENITAL HORIZONTAL TARSAL KINK

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Because of its rare occurrence, congenital entropion is infrequently recognized as a cause of corneal ulcers in infants. Delayed recognition and treatment may result in permanent visual impairment. We describe a case of a boy who had an extreme form of entropion caused by a congenital horizontal tarsal kink,[1] which led to corneal ulceration and visual impairment.

CASE REPORT

A 3-week-old irritable male infant was referred for treatment of an ulcerated cornea that was observed on the fifth day of life. The ulcer was superficial and was initially treated with topically administered gentamicin. The many cultures obtained were either sterile or yielded small quantities of coagulase positive *Staphylococcus*.

The poor clinical response of the ulcer prompted transfer of the child to Children's Hospital of Pittsburgh. Examination at the time of admission showed an irritable child with severe blepharospasm and absence of the eyelid fold on the right upper eyelid (Fig. 1). A geographic central corneal ulcer was observed on the right eye. Normal anterior chamber and iris structure were noted. The left eye was normal. Cultures obtained after suspension of topically administered antibiotics yielded small quantities of mannitol-positive *Staphylococcus* but no *Neisseria* species. Topically administered gentamicin, polymyxin B sulfate (Neosporin), and cyclopentolate HCl resulted in slow epithelialization of the ulcer. An allergic response developed and bacitracin ophthalmic ointment was substituted. The ulcer continued to epithelialize and the patient was discharged on the tenth hospital day.

One week after discharge, the patient was observed in a resting state for the first time. An obvious entropion of the right upper eyelid was noted, which was not able to be reduced. The following day surgical repair was done.

Examination at the time of the operation showed a horizontal kink that spanned the entire length of the superior tarsal plate and produced inversion of the distal 3 mm of the right eyelid margin (Fig. 2). The kink was elastic and would not remain reduced when the distal portion of the tarsus was placed in its normal position. A skin incision was made in the position of an eyelid fold and the tarsus was surgically fractured with a sharp dissection at the apex of the crease. Everting sutures were placed through both edges of the tarsus and passed through the skin and tied over bolsters, thereby creating an upper eyelid fold and placing the distal tarsal margin in a normal position.

The first postoperative examination showed a resting child who had a normal feeding pattern. The corneal ulcer was completely epithelialized and the stromal opacity was clearing at its peripheral margins.

Fig. 1 (Biglan and Buerger). Congenital tarsal kink associated with absence of the upper eyelid fold.

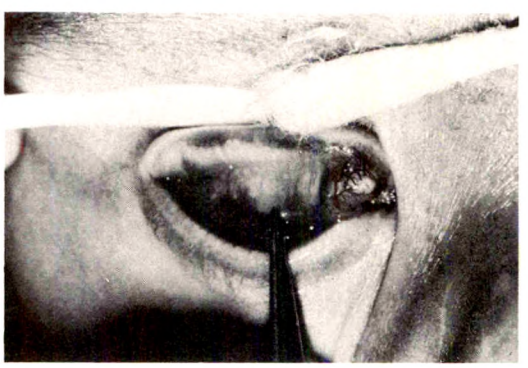

Fig. 2 (Biglan and Buerger). Everted right upper eyelid. The forceps are grasping the superior edge of the tarsus. Cotton-tipped applicators are necessary to reduce the tarsal kink.

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Sixteen months after repair, the patient has a 3-mm corneal opacity in the visual axis. The patient is being treated with phenylephrine and occlusion therapy. Fixation, however, remains unsteady.

Discussion

Congenital entropion occurs rarely; only 13 cases were reported before 1969.[2] Congenital horizontal tarsal kink[1] represents an extreme form of this condition. Entropion in infants must be distinguished from epiblepharon, a condition characterized by a fold of skin that pushes the eyelashes of the lower eyelid toward the globe and cornea. Epiblepharon usually resolves spontaneously and rarely requires surgical intervention.

Congenital entropion, or its extreme form, horizontal tarsal kink, is characterized by a fixed inward rotation of the distal tarsal margin causing cilia to abrade the cornea. This inverted upper eyelid margin may be caused by an overaction of the marginal orbicularis fibers, or as in this case, a kink is present in the tarsus.

Congenital entropion has been associated with several systemic defects that include the following: cardiac defects, mental retardation, skull defects, brachysyndactly, equinovarus, and micrognathia,[2] and some of these may delay diagnosis and the timing of surgical intervention.

Previous treatments for congenital entropion include the following: lateral canthotomy,[3] the Celsus procedure,[4] oblique blepharotomy and Snellen suture,[5] simple excision of the tarsus,[6] excision of the tarsal kink, and a modified Panas' operation.[7]

Our patient had a unilateral kink in the upper tarsus that caused a corneal ulcer. The kink was associated with the absence of an upper eyelid fold and severe blepharospasm. A review of all available preoperative photographs of previous case reports of infants with congenital entropion shows that a total absence of the upper eyelid fold or the presence of only a vestigial remnant is common to all.[1,2,8] Blepharoptosis, which is usually associated with the absence of an eyelid fold, was not present.

Our patient was similar to the one described by Callahan.[1] Both of these patients had a persistent kink defect even when the orbicularis was relaxed under general anesthesia. A Celsus procedure or simple excision of orbicularis and skin would not have been sufficient to hold the eyelid in an everted position without placing undue stress on the skin incision.

The procedure advocated by Callahan,[1] specifically for reducing a tarsal kink, involves resection of the kink and everting the eyelid with matress sutures. This may produce a shortening of the eyelid. We elected to use a tarsal splitting procedure as advocated by Wies[9] and later applied to the upper eyelid by Ballen.[10] This procedure is commonly used to correct cicatricial entropion in adults and the ophthalmic surgeon's familiarity with this procedure, as well as its predictability, make it an ideal procedure for correcting entropion of this degree in infants. Use of this procedure resulted in an excellent functional and cosmetic result in our patient.

Congenital entropion is one of the causes for corneal ulceration in infants. In our patient, the delay in recognition of this entity may have caused a permanent visual deficit. We believe that infants with corneal ulcers should have appropriate cultures obtained and antibiotics initiated when indicated. We also would advise that the ophthalmologist observe the child at rest if possible.

Summary

A 3-week-old male infant had an extreme form of entropion caused by a congenital horizontal tarsal kink, which led to corneal ulceration and visual impairment. The combination of absence of the upper eyelid fold, irritability, and blepha-

rospasm in the absence of congenital blepharoptosis is a sign that may facilitate early recognition of this problem.

ACKNOWLEDGEMENT

John Wick, M.D., referred this patient to us.

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OPHTHALMIC MINIATURE

Fifty years ago this month in The Journal

A well-performed combination of iridencleisis and sclerectomy will almost invariably yield a good filtering cicatrix, and almost always without the aid of massage. With the exception of two cases, my results with this operation have been extremely satisfactory, and I have performed the operation several times on an only eye, the other having been previously lost from untreated glaucoma. All of these one-eyed patients have done well, and several of them have returned to their occupations. As one method of producing a filtering cicatrix in cases of chronic glaucoma I commend it to your consideration. I have never seen a case of hypotony follow this operation.

Combined iridencleisis and
sclerectomy for chronic
glaucoma, by A. Greenwood
Am. J. Ophthalmol. 13:302, 1930

COMBINED Z-PLASTY AND HORIZONTAL SHORTENING PROCEDURE FOR ECTROPION

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Acquired, senile ectropion is usually caused by horizontal laxity of the eyelid and can be successfully treated with a horizontal shortening operation. Cicatricial ectropion is secondary to a vertical loss of skin and is treated with a Z-plasty of the eyelid skin, if the vertical shortage of skin is in one eyelid segment, or with a skin graft if the shortage is diffuse.

Occasionally, an ectropion of the eyelid is secondary to both vertical loss of skin and horizontal laxity of the eyelid. In such cases, treatment only of the horizontal laxity or of the cicatricial component will frequently leave some residual ectropion of the eyelid. Therefore, if the skin shortage is diffuse, treatment consists of a skin graft combined with a full-thickness pentagonal resection of eyelid tissue.[1] If this skin cicatrix is localized to one third of the eyelid, the ectropion can be treated with a skin Z-plasty performed simultaneously with a full-thickness pentagonal horizontal shortening procedure.

Described herein is a combined Z-plasty and horizontal shortening procedure to treat ectropions with cicatricial and horizontal laxity components. To the best of my knowledge, this is the first report of this technique, which has successfully relieved ectropions in six patients.

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MATERIAL AND METHODS

A methylene blue marking pen is used to draw a vertical line from the eyelid margin to a distance about 10 mm from the margin, approximately 6 mm temporal to the scarred eyelid (Fig. 1, A). A nasal oblique line is then drawn from the end of the first line toward the inferior apex of the scar. The scarred area can be determined by palpation as well as by resistance to elevation of the lower eyelid or depression of the upper eyelid with the surgeon's finger.

Local or general anesthesia can be used. If local, approximately 3 ml of 2% lidocaine (Xylocaine) with epinephrine is injected subcutaneously over the involved eyelid. Topically administered tetracaine is instilled over the cornea, and a scleral lens is inserted over the eye to protect it during the procedure.

A No. 11 Bard-Parker blade is used to sever the full-thickness eyelid over the vertical methylene blue line temporal to the scar. The blade enters the eyelid about 4 mm from the eyelid margin, penetrates the full-thickness eyelid, and then, with a slicing motion, creates a sharp, clean vertical cut through the eyelid margin. The knife blade is reversed and is used to sever the full-thickness eyelid to the end of the vertical line. The full-thickness eyelid is then severed with a Westcott scissors along the oblique methylene blue line in a nasal inferior direction, beginning at the end of the first vertical incision and terminating beneath the inferior scar apex.

The contact lens is removed, and the

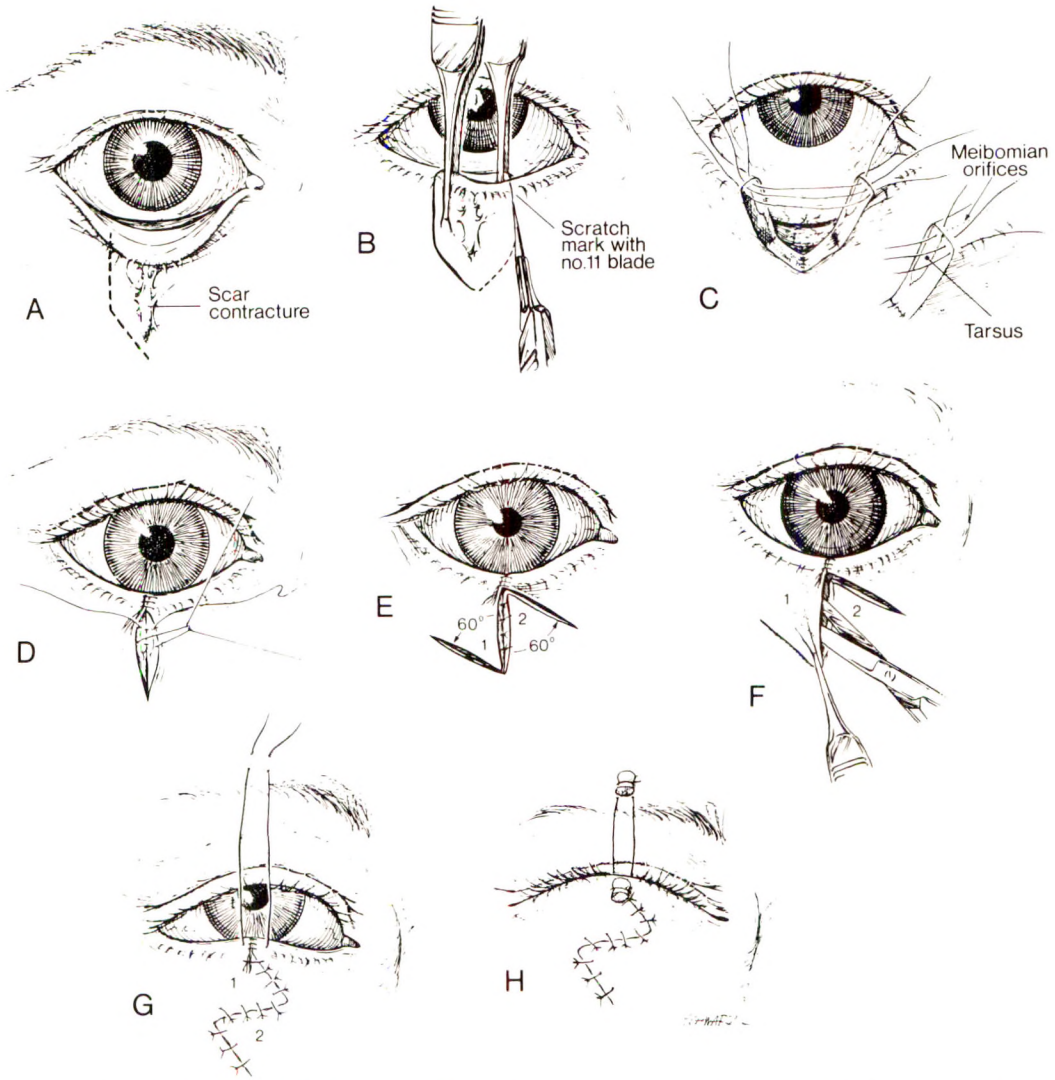

Fig. 1 (Putterman). A, Dotted line indicates site of temporal vertical and inferior oblique sides of full-thickness pentagonal resection. B, Forceps overlap the eyelid segments to slight tension. C, Three sutures unite eyelid margin. D, Eyelid margin sutures are tied, and ends of internal two sutures are tied over the cilia suture ends. Superficial tarsus, pretarsal fascia, and orbicularis muscle are sutured. E, Z-plasty incisions. F, Nasal and temporal Z-plasty skin flaps are dissected from underlying orbicularis muscle. G, Transposition and suturing of skin flaps. Tarsorrhaphy suture is placed through eyelid margin. H, Tarsorrhaphy suture is passed above central eyebrow and tied over cotton pledget.

eyelid margin is grasped with two-toothed forceps on either side of the eyelid vertical incision. By grasping the eyelid several millimeters below the eyelid margin and several millimeters on either side of the incision, the margin and the incision sites are not crushed, which could interfere with suturing and healing. The forceps are pulled in opposite directions so that the eyelid remnants on each side of the incision are overlapped (Fig. 1, B). A scratch incision is made on the eyelid margin at the site that the eyelid rem-

nants are overlapped to the extent of slight tension (Fig. 1, B).

The contact lens is replaced on the eye. A No. 11 Bard-Parker blade is used to incise the full-thickness eyelid and eyelid margin in a 10-mm vertical cut at the location of the scratched eyelid margin in a similar manner to the previous temporal vertical incision. The pentagonal resection is completed with a temporal inferior oblique cut with Westcott scissors, beginning at the inferior end of the nasal vertical cut and connecting with the inferior extent of the previous incision site at the apex of the scar. In this way, a full-thickness pentagon of redundant eyelid that includes the scarred segment of the eyelid is removed.

The eyelid margin is then united with three 6-0 black silk double-armed sutures (Fig. 1, C). One arm of each suture is placed through the tarsus to exit at the squared corner where conjunctiva meets the eyelid margin. The second suture is placed through the gray line, and the third is placed through the most internal row of cilia. Sutures are tied in triplicate, and the cilia suture ends are tied over the four internal suture ends. In this way, when all six ends are cut lengthwise, they point away from the cornea to avoid keratopathy (Fig. 1, D). Four to six 6-0 polyglactin 910 (Vicryl) sutures then pass through the superficial tarsus, pretarsal fascia, and orbicularis muscle to unite the vertical incision (Fig. 1, D). The eyelid margin sutures are pulled upward by a hemostat, with minimal tension.

A methylene blue marking pen is then used to draw the lines for the Z-plasty incision. One line is drawn 60 degrees from the vertical incision, beginning at its superior end, and extending for a distance equivalent to the length of the slightly stretched vertical incision (Fig. 1, E). The second line is drawn from the inferior end of the vertical incision, and 60 degrees from it in a direction on the other side of the vertical incision, again for a distance equivalent to the vertical incision length (Fig. 1, E). Whether the superior or inferior incision is nasal or temporal will depend on the skin available for flaps in those directions.

A No. 15 Bard-Parker blade incises the skin over the methylene blue line (Fig. 1, E). The temporal and nasal skin flaps are undermined from underlying orbicularis muscle with sharp-pointed iris scissors (Fig. 1, F). Observing the points of the scissors through the translucent skin during the dissection eliminates buttonholing the skin and avoids including subcutaneous tissue with the flaps. The flaps are overlapped. If there is much tension, the skin adjacent to the flaps is undermined until the flaps can be overlapped with minimal tension. Bleeding is controlled with disposable cautery. The flaps are then transposed so that the superior flap is brought to the inferior position and the inferior flap to the superior area (Fig. 1, G). The flaps are then sutured to surrounding skin with interrupted 6-0 black silk sutures (Fig. 1, G).

A 4-0 black silk double-armed suture is placed in the eyelid on each side of the sutured eyelid margin. Each suture enters skin about 4 mm from the eyelid margin, passes through the orbicularis oculi muscle and superficial tarsus, and exits at the gray line (Fig. 1, G). The ends of each suture then pass through the forehead above the central eyebrow, if the lower eyelid is being operated on, or the central cheek if the upper eyelid is ectropic. The contact lens is removed, and the 4-0 black silk suture is tied over small cotton pledgets so that the eyelid is stretched to slight tension (Fig. 1, H).

After six to seven days the skin sutures are removed. After 12 to 14 days the eyelid margin and tarsorrhaphy sutures are removed. Two and one-half to three weeks postoperatively, the patient be-

gins massaging the lower eyelid in an upward direction or the upper eyelid in a downward direction, over the incision site. This is continued for one month.

Discussion

Cicatricial ectropion of the eyelid is usually caused by vertical loss of skin from trauma, previous surgery, or burns. Diagnosis of lower eyelid cicatricial ectropion can be aided by the palpation of scar tissue in the eyelid. The ectropion will also be accentuated when the patient opens the mouth widely. This places a stretch on the facial skin. There will also be minimal eyelid elevation on upgaze. In upper eyelid cicatricial ectropion, there is usually eyelid lag, eyelid retraction, and lagophthalmos.

If the eyelid margin is relatively tight, cicatricial ectropion can be relieved with a skin Z-plasty, if associated with localized cicatricial changes, or a skin graft, if associated with diffuse scarring.

An acquired senile lower eyelid ectropion is usually the result of stretching of all the eyelid tissue components, which results in horizontal eyelid laxity. The diagnosis of an ectropion caused by horizontal laxity can be made by ruling out a history of trauma, previous surgery, and burns. The absence of ectropion accentuation on opening the mouth widely, the inability to palpate scar tissue within the eyelid, the ease of lower eyelid elevation or upper eyelid depression, and the ability to pinch the horizontally redundant full-thickness eyelid together further aid in the diagnosis. This type of ectropion can usually be easily corrected by tightening the lower eyelid in a horizontal direction by removing a section of full-thickness eyelid.[2]

Occasionally, a cicatricial ectropion occurs simultaneously with horizontal laxity of the eyelid. If only a Z-plasty or skin graft is performed, the patient may still retain a partial ectropion. The diagnosis is made by finding characteristics of both cicatricial and acquired ectropion occurring together. I have had several patients who retained an ectropion after I have performed a Z-plasty for a cicatricial ectropion that occurred after surgery for eyelid cancer. Resection of a full-thickness section of the horizontally lax eyelid as a second procedure corrected the residual ectropion in these cases.

To correct a lower eyelid ectropion secondary to cicatricial and horizontal eyelid laxity components, a skin graft can be combined with a full-thickness pentagonal resection if the cicatricial changes are diffuse and encompass more than one third of a horizontal eyelid dimension.[1] If the cicatrix is confined to a segment of the eyelid less than one third in horizontal dimension, a skin Z-plasty can be combined with a full-thickness pentagonal resection.

Resection of full-thickness eyelid not only tightens the eyelid horizontally, but also eliminates the cicatricial section of the eyelid that is causing the cicatricial ectropion component. In some cases, this resection is probably all that may be needed to eliminate both horizontal and cicatricial ectropion components. However, because more vertical cicatricial changes are likely to occur after resecting full-thickness eyelid, a Z-plasty is added to the horizontal shortening to help ensure a successful result.

Some patients with cicatricial ectropion have an abnormal eyelid margin secondary to a previous traumatic laceration that was poorly repaired. In these cases, even if the eyelid is not horizontally lax, the full-thickness eyelid resection combined with the Z-plasty corrects the abnormal eyelid margin and cicatricial ectropion simultaneously.

A combined horizontal shortening and Z-plasty procedure has successfully eliminated lower eyelid ectropion caused by horizontal laxity and vertical cicatrix in four patients. It has been successful in relieving upper eyelid ectropion associat-

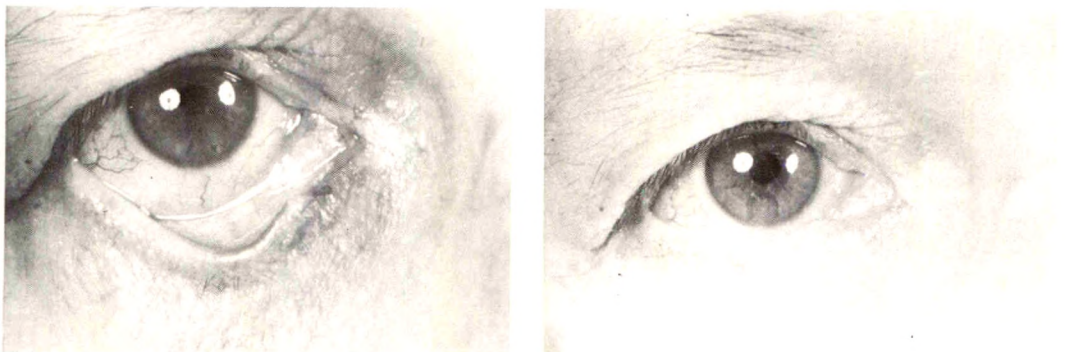

Fig. 2 (Putterman). Left, Right lower eyelid cicatricial ectropion with horizontal eyelid laxity after excision of basal cell cancer. Right, Correction of ectropion six months after Z-plasty horizontal shortening procedure.

ed with eyelid retraction, lagophthalmos, eyelid lag, keratopathy, and abnormal eyelid margins in two other patients.

Two of the patients with lower eyelid ectropion had had lower eyelid basal cell cancer surgery, in which skin and subcutaneous tissue were removed. In one patient a skin graft had been placed; in another patient no graft was used during the primary surgery (Fig. 2). A third patient with lower eyelid ectropion had suffered a traumatic laceration and avulsion of the lower eyelid as well as a laceration of eye that required enucleation. The fourth patient had neurofibromatosis, which led to horizontal laxity of the lower eyelid and secondary ectropion; the cicatricial component was caused by a surgical burn of the eyelid skin that occurred while holes were being drilled in the inferior orbital rim to fixate an orbital floor implant. The cicatrix from the dissection of skin from orbicularis oculi muscle during the surgical placement of the implant also added to the ectropion in this patient.

The two patients with upper eyelid ectropion had suffered trauma in automobile accidents that led to laceration and avulsion of parts of the upper eyelids. In one patient, the eyelid was horizontally tight but the eyelid margin was abnormal because of an inadequately repaired eyelid margin (Fig. 3, left). The prescribed

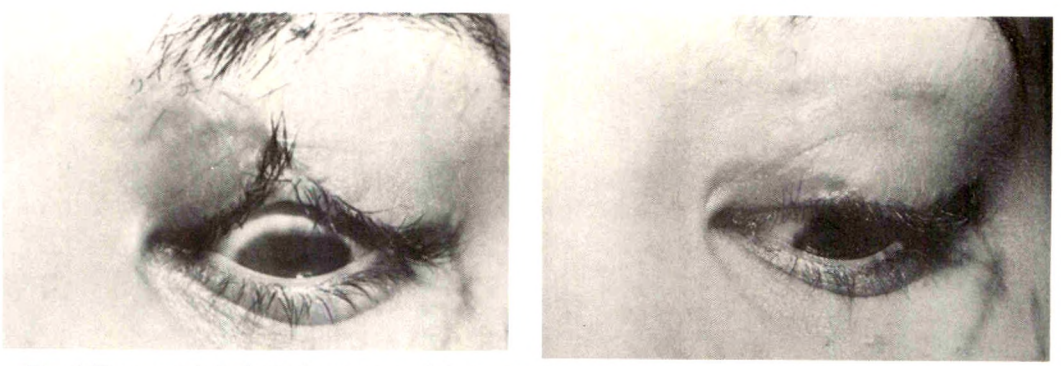

Fig. 3 (Putterman). Left, Right upper eyelid cicatricial ectropion associated with abnormal eyelid margin, eyelid lag, lagophthalmos, and keratopathy after eyelid laceration from an automobile accident. Right, Resolution of right upper eyelid ectropion, eyelid lag, lagophthalmos, and keratopathy, and restoration of normal eyelid margin four months after Z-plasty horizontal shortening procedure.

procedure not only relieved the ectropion, eyelid lag, lagophthalmos, and keratopathy, but created a more normal eyelid margin (Fig. 3, right). The second patient with upper eyelid ectropion suffered a corneal ulcer caused by severe lagophthalmos associated with the cicatricial ectropion. He had slight horizontal laxity of the eyelid. However, the main purpose of the full-thickness pentagonal resection of the upper eyelid was to eliminate the severely scarred segment of the eyelid.

Summary

A combined Z-plasty and horizontal shortening procedure to treat ectropions with cicatricial and horizontal laxity components successfully relieved ectropions in six patients.

If the cicatricial changes are localized to one third or less of the eyelid, a skin Z-plasty to vertically lengthen the eyelid can be combined with a full-thickness pentagonal resection to horizontally tighten the eyelid.

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VARIABLE EXPRESSIVITY IN AUTOSOMAL DOMINANT ANIRIDIA BY CLINICAL, ELECTROPHYSIOLOGIC, AND ANGIOGRAPHIC CRITERIA

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Autosomal dominant aniridia associated with nystagmus, corneal pannus, cataracts, ectopia lentis, glaucoma, macular hypoplasia, optic nerve hypoplasia, and generally compromised ocular function has been well documented.[1,2] Numerous reports have described the markedly variable expression of dominant aniridia mutations, showing iris thinning, typical and atypical colobomas, and relatively complete aniridia within individual families.[3–13] Recently, one family with aniridia was described with preserved visual acuity and a decrease in the number and severity of the commonly associated features.[13] We describe a family with autosomal dominant aniridia characterized by highly variable iris abnormalities, preserved ocular function, the variable presence of nystagmus, corneal pannus, cataracts, glaucoma, macular hypoplasia, or optic nerve hypoplasia, diverse electrophysiologic recordings, and diagnostic angiographic findings.

SUBJECTS AND METHODS

Fifteen individuals in four generations of a single family were shown by examination to have aniridia, and one more was ascertained by review of ophthalmologic records. Additionally, 18 unaffected relatives were examined. Only five relatives, all reportedly unaffected, were not examined. All 15 living affected family members were examined on site in the Texas Medical Center and had the following examinations: visual acuity best corrected by refraction, external examination, motility examination, slit-lamp examination noting expecially iris configuration and presence of small and large amplitude nystagmus, anterior segment photographs, applanation tonometry, examination by direct and indirect ophthalmoscopy, and fundus photography. Fourteen patients had electroretinograms and visual-evoked response testing, ten had electro-oculograms, 13 had 100-hue color testing, 12 had Goldmann visual field testing, nine had iris angiography, and eight had fundus angiography.

RESULTS

In the family pedigree shown in Figure 1, the segregation of aniridia is consistent with an autosomal dominant inheritance pattern, although there is no male-to-male transmission. Of the 16 affected members, nine are females and seven are males. Approximately 50% of the people at risk are affected (15/30). In other families[1,2] far fewer than 50% of the people at risk have been affected, perhaps because careful slit-lamp examinations of all at-risk family members were not performed.

Summary of clinical findings is presented in the Table. Of the 16 affected family members, ten had visual acuity of 6/12 (20/40) or better in at least one eye (63%), and six had visual acuity from 6/15

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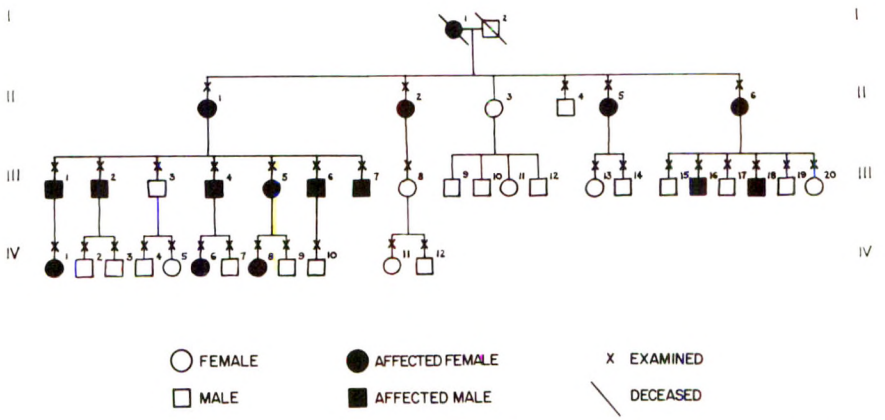

Fig. 1 (Hittner and associates). Pedigree of family with autosomal dominant aniridia with variable expressivity.

(20/50) to 6/60 (20/200) in at least one eye (37%). Nystagmus was present in 12 patients (75%), cataracts in nine patients (56%), strabismus in 15 patients (94%), amblyopia in six patients (37%), corneal pannus in one patient (6%), glaucoma in one patient (6%), macular hypoplasia in five patients (31%), and optic nerve hypoplasia in one patient (6%). No patient had any extraocular anomalies. Specifically, no affected family member was mentally retarded, or had genitourinary or dental anomalies.

The extreme variability in the appearance of the iris is shown in Figure 2. Complete or near complete aniridia was present in six patients (37%). Colobomas that were typical (with additional areas of thinning) or atypical occurred in seven eyes of four patients. Round pupils with minimal iris thinning were present in 13 eyes of seven patients (41%), although one of these patients had severe corneal pannus bilaterally. Fluorescein angiography of the iris was performed on many family members. The abnormal findings in patients with colobomas and iris thinning included early filling of vascular loops (Fig. 3, top left and bottom left) followed by the appearance of more iris vessels and leakage of dye at the pupillary margin (Fig. 3, top right and bottom right).

Macular hypoplasia was noted in all family members with visual acuity of 6/15 (20/50) or less in their better eye, except for the patient with bilateral severe corneal pannus. Several small white spots of unknown nature were also noted in the fundi of many patients. Figure 4,A and B compares the appearance of the macular regions in the eyes with normal visual acuity of 6/6 (20/20) and impaired visual acuity of 6/24 (20/80). The small white spots are shown in Figure 4,B. The macular areas, best studied by fluorescein angiography, were abnormal in patients wih normal visual acuity of 6/6 (20/20) and impaired visual acuity of 6/60 (20/200) (Fig. 5). The patient with visual acuity of 6/6 (20/20) and the patient with visual acuity of 6/60 (20/200) had markedly decreased avascular zones in the areas where the maculae would be anticipated. In all eight affected patients who had fluorescein angiography, fundi were considered abnormal by virtue of capillaries being present in the usually avascular macular zones. The small white spots were not well delineated on angiography, although several noncorresponding small hyperfluorescent spots were seen in the same region, as shown in Figure 5, right.

Those patients with macular hypoplasia and visual acuity of 6/21 (20/70) or 6/24

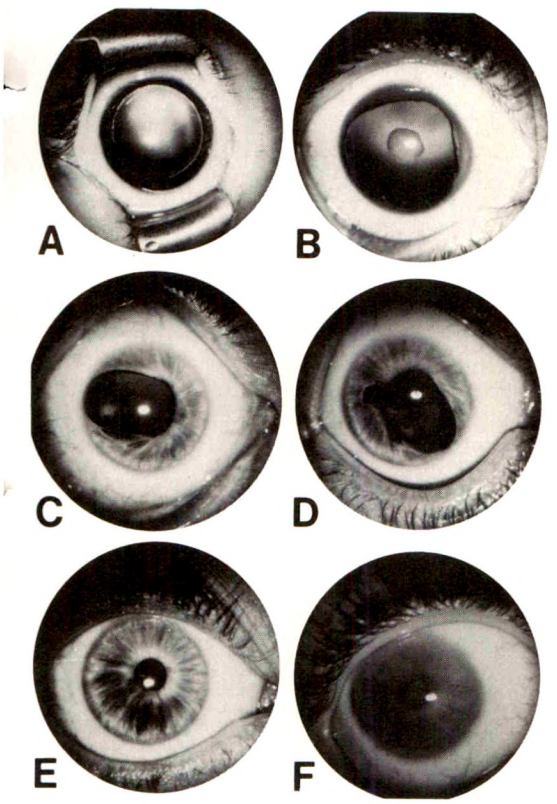

Fig. 2. (Hittner and associates). Variable appearance of anterior segment of right eye in affected family members. (A) Case IV-1; Virtually total aniridia; (B) Case II-6, Small amount of iris visible; (C) Case III-2, Atypical coloboma of iris; (D) Case III-5, Typical coloboma of iris with additional areas of iris thinning; (E) Case III-7, Iris thinning with round pupil; (F) Case III-18, Corneal pannus with iris thinning with round pupil.

(20/80) in their better eye had markedly decreased electroretinogram signal amplitudes and prolonged latencies of the b-wave peaks (implicit times), as shown in Figure 6,A. Most other affected family members had abnormal electroretinograms with either a high a:b-wave ratio (Fig. 6,B), or an unusually high signal amplitude (Fig. 6,C), but in these patients b-wave latencies were normal. The electro-oculograms of several patients were all normal or showed only slight high or low variations from the normal range. The visual-evoked responses of multiple family members were usually atypical in wave form, though no consistent abnormality was identified.

Discussion

A classification of aniridia should include the following: (1) autosomal dominant forms,[1,2] (2) autosomal recessive cases,[14–17] and (3) sporadic cases often associated with Wilm's tumor and the 11 p chromosomal deletion.[18] The differential diagnosis of aniridia must include simple colobomas and colobomatous microphthalmia that occur earlier in embryogenesis and are associated with colobomas of the choroid, retina, and optic nerve. The various anterior cleavage syndromes may be confused with aniridia, but because they reflect defects occurring later in embryogenesis and are associated with prominent Schwalbe's lines and iris adhesions to Schwalbe's line and to the posterior cornea, they are readily differentiated. Each of these types of disorders can be inherited as autosomal dominant traits or can occur sporadically, and they may be associated with other systemic anomalies. In the present family, no patient had an isolated simple coloboma of the iris, nor a coloboma of the choroid, retina, or optic nerve. Further, no family member had any abnormality commonly associated with the anterior cleavage syndromes, such as prominence of Schwalbe's line, or iris adhesions to Schwalbe's line or to the posterior cornea.

This family's autosomal dominant aniridia is characterized by variable expressivity.[3–13] Before this study, many members were not aware of the diagnosis in their own family, and many affected family members were so slightly involved that they did not realize that they had any ocular abnormality whatsoever. They clearly did not realize that they were at risk for having severely affected children. Cases III-4, III-6, III-7, III-16, and IV-8 were all unaware that they carried a gene for aniridia, because each of them had round pupils and at least one eye with

TABLE

CLINICAL FINDINGS IN PEDIGREE WITH AUTOSOMAL DOMINANT ANIRIDIA WITH VARIABLE EXPRESSIVITY*

Case No.	Date of Birth Sex	Visual Acuity		Nystagmus	Iris Appearance	Fundus Appearance
		Right Eye	Left Eye			
I-1‡	3/4/05 F	6/60 (20/200)	6/60 (20/200)	Present	Aniridia	Macular hypoplasia
II-1	10/7/30 F	6/12 (20/40)	6/120 (20/400)	Present	Iris remnant	Normal macula
II-2	4/23/33 F	6/12 (20/40)	6/120 (20/400)	Present	Iris remnant	Normal macula
II-5	7/7/42 F	6/9 (20/30)	6/9 (20/30)	Absent	Iris remnant	Normal macula
II-6	4/15/45 F	6/12 (20/40)	6/12 (20/40)	Absent	Iris remnant	Normal macula
III-1	5/30/48 M	6/21 (20/70)	6/30 (20/100)	Present	Right eye§ left eye§	Macular hypoplasia
III-2	11/17/49 M	6/60 (20/200)	6/24 (20/80)	Present	Atypical coloboma	Macular hypoplasia
III-4	10/18/52 M	6/9 (20/30)	6/15 (20/50)	Present	Only iris thinning	Normal macula
III-5	11/23/54 F	6/15 (20/50)	6/120 (20/400)	Present	Typical coloboma	Macular hypoplasia
III-6	9/12/58 M	6/7.5 (20/25)	6/7.5 (20/25)	Absent	Only iris thinning	Normal macula
III-7	9/7/61 M	6/12 (20/40)	6/6 (20/20)	Absent	Only iris thinning	Normal macula
III-16	10/6/65 M	6/12 (20/40)	6/18 (20/60)	Present	Only iris thinning	Normal macula
III-18	2/17/68 M	Hand movements	6/60 (20/200)	Present	Only iris thinning	Normal macula
IV-1	12/1/77 F	6/12 (20/40)	6/12 (20/40)	Present	Aniridia	Normal macula
IV-6	2/5/74 F	6/18 (20/60)	6/18 (20/60)	Present	Typical coloboma	Macular hypoplasia
IV-8	4/26/72 F	6/9 (20/30)	6/9 (20/30)	Present	Only iris thinning	Normal macula

*EOG designates electro-oculogram; VER, visual-evoked response; ND, not done; N, normal; and A, abnormal.

†Electroretinogram (μV in right and left eye averaged).

‡This patient died two years previously, but relatively complete ophthalmologic records were available for review.

§Right eye, typical coloboma; left eye, only iris thinning.

‖Unilateral cataract extraction performed.

¶Bilateral cataract extraction performed.

#Was amblyopic before patching.

visual acuity of 6/12 (20/40) or better. Four of these patients had esotropia and one had exotropia, and all had been examined for these conditions without recognition of their abnormally thinned irides. The iris abnormality is particularly difficult to recognize without the aid of a slit lamp and is less frequently identified when the irides are brown as in Case III-16.

Iris involvement in all cases was relatively symmetrical except for Case III-1

TABLE *(Continued)*

CLINICAL FINDINGS IN PEDIGREE WITH AUTOSOMAL DOMINANT ANIRIDIA WITH VARIABLE EXPRESSIVITY*

Strabismus	Cataracts	Visual Field	a:b-Wave Ratio†	EOG	VER	Secondary Complication
Esotropia	Present	ND	ND	ND	ND	Macular hypoplasia, both eyes
Exotropia	Present‖	A	24:43	N	A	Cataract, left eye
Exotropia	Present¶	A	25:42	A	A	Glaucoma, left eye
Orthophoria	Present‖	A	ND	ND	ND	—
Esotropia	Present	N	29:55	N	A	—
Exotropia	Present	N	3:5	A	A	Macular hypoplasia, right eye; amblyopia, left eye
Esotropia	Absent	A	9:17	A	N	Amblyopia, right eye; macular hypoplasia, left eye
Esotropia	Absent	N	27:55	N	N	Amblyopia, left eye
Esotropia	Present	A	26:36	ND	A	Macular hypoplasia, right eye; amblyopia, left eye
Exotropia	Present	N	18:27	N	N	—
Esotropia	Absent	N	17:37	N	A	Amblyopia, right eye
Esotropia	Absent	A	19:33	N	A	Optic nerve hypoplasia, left eye
Exotropia	Present	ND	29:47	N	A	Amblyopia, right eye; corneal pannus, left eye
Esotropia	Absent	ND	16:19	ND	A	—
Esotropia	Absent	ND	20:37	ND	A	Macular hypoplasia, both eyes
Esotropia	Absent	N	23:38	ND	A	—#

who had a typical coloboma of the right iris but only iris thinning of the left iris. Visual acuity, however, was often unequal. In the two individuals with visual acuity differences between their eyes identified before age 10 years, the visual acuity of the amblyopic eyes improved to that of the fellow eyes by conventional patching. Case IV-6 had a typical coloboma of each iris and at age 4 years had visual acuity of R.E.: 6/30 (20/100) and L.E.: 6/18 (20/60). She also had hypermetropia and esotropia. Conventional glass correction and patching produced visual acuity of 6/18 (20/60) in both eyes. Case IV-8 had a round pupil with minimal thinning and visual acuity of R.E.: 6/9 (20/30) and L.E.: 6/120 (20/400) when first examined at age 6 years. She also had hypermetropia and esotropia, and conventional spectacle correction and patching increased her visual acuity to 6/9 (20/30) in both eyes. It is thus important in cases of aniridia in which the visual acuities are unequal to treat for amblyopia.

Case III-18 shows the possibility of corneal pannus being the initial symptom of autosomal dominant aniridia.[19] His

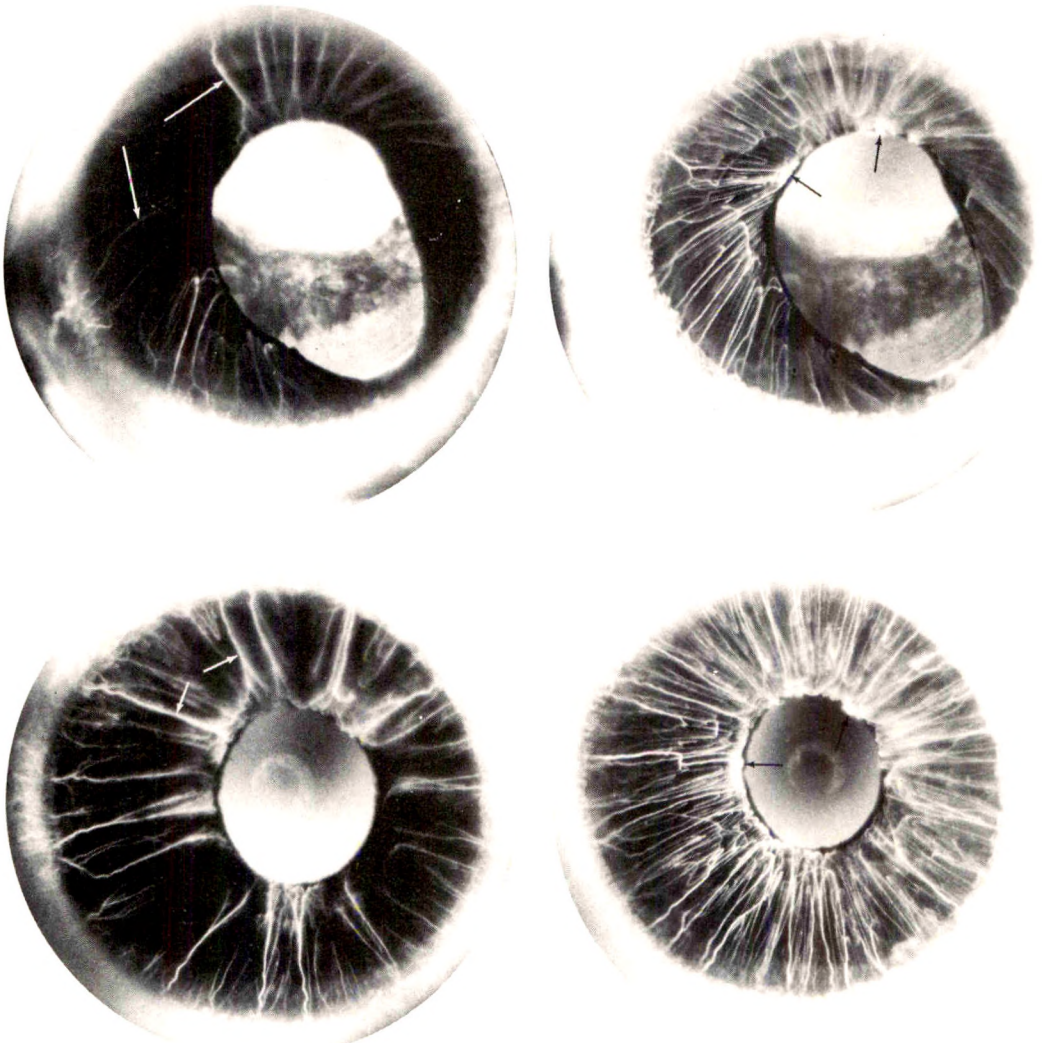

Fig. 3 (Hittner and associates). Anterior segment fluorescein angiography of affected family members. Top left, Case III-5, Typical coloboma of iris with additional areas of iris thinning (right eye). Arrows mark vascular loop at 19.5 seconds after injection of dye. Top right, Case III-5, Arrows mark areas of dye leakage at 30.9 seconds after injection (right eye). Bottom left, Case IV-8, Iris thinning with round pupil (right eye). Arrows mark vascular loop at 14.2 seconds after injection of dye. Bottom right, Case IV-8, Arrows mark areas of dye leakage at 22.6 seconds after injection (right eye).

mother had near complete aniridia and cataracts and he was a regular visitor to a children's eye clinic, yet there was no recognition that his condition represented a variant of aniridia. Further, the mother had never been told that her diagnosis was aniridia because her visual acuity was 6/12 (20/40) in each eye, and such good visual acuity was not believed to be compatible with classic aniridia.

Case IV-6 had an area of gliosis adjacent to one optic nerve (Fig. 4, C). Case III-16 represents a case of unilateral hypoplastic optic nerve associated with hypoplasia of the iris (Fig. 4, D). Optic nerve hypoplasia has been recognized as a commonly associated finding in cases of aniridia.[20]

Fluorescein angiography of the anterior segment was used to study the abnormal iris vessels in the variable iris anomalies of the affected family members. These

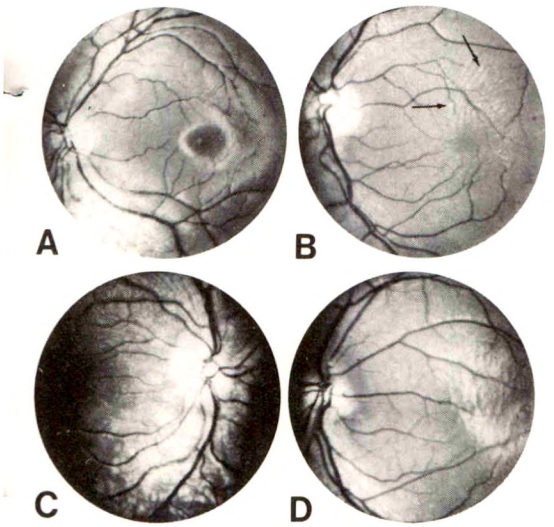

Fig. 4 (Hittner and associates). Fundus photographs of affected family members. (A) Case III-7, Good foveal reflex associated with 6/6 (20/20) visual acuity (left eye). (B) Case III-2, Decreased foveal reflex associated with 6/24 (20/80) visual acuity (left eye). Note small white spots marked by arrows. (C) Case IV-6, Glial tissue adjacent to optic nerve in eye with 6/18 (20/60) visual acuity (right eye). (D) Case III-16, Hypoplastic optic nerve in eye with 6/18 (20/60) visual acuity (left eye).

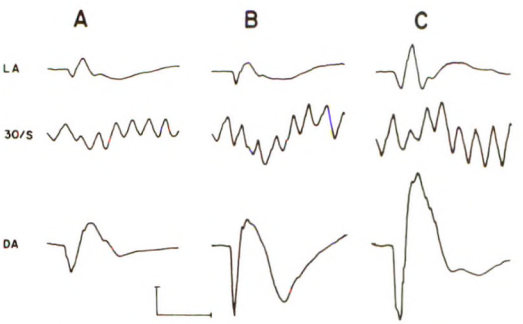

Fig. 6. (Hittner and associates). Electroretinograms of affected family members. (A) Case III-2, Decreased amplitude and prolonged latency of the b-wave peak (implicit time) of the electroretinogram in left eye with 6/24 (20/80) visual acuity; (B) Case III-5, Abnormal a:b-wave ratio in right eye with 6/15 (20/50) visual acuity. Latency of the b-wave is normal; (C) Case III-4, Increased amplitude of electroretinogram in right eye with 6/9 (20/30) visual acuity. Latency of the b-wave is normal; LA indicates photopic response; 30/s, flicker response; DA, scotopic response. Vertical calibration = 100 μV; horizontal calibration = 100 msec.

included early vascular loops and late leakage of dye from the pupillary margin. This technique was especially useful in studying brown irides with round pupils because usually such irides do not reveal the fluorescein dye well.

Fluorescein angiography of the posterior segment was performed to show persistence of vessels in the normally avascular area of the macula in affected patients. It was also used to assist in an attempt to delineate the small white spots seen in the fundi of several patients. However, fluo-

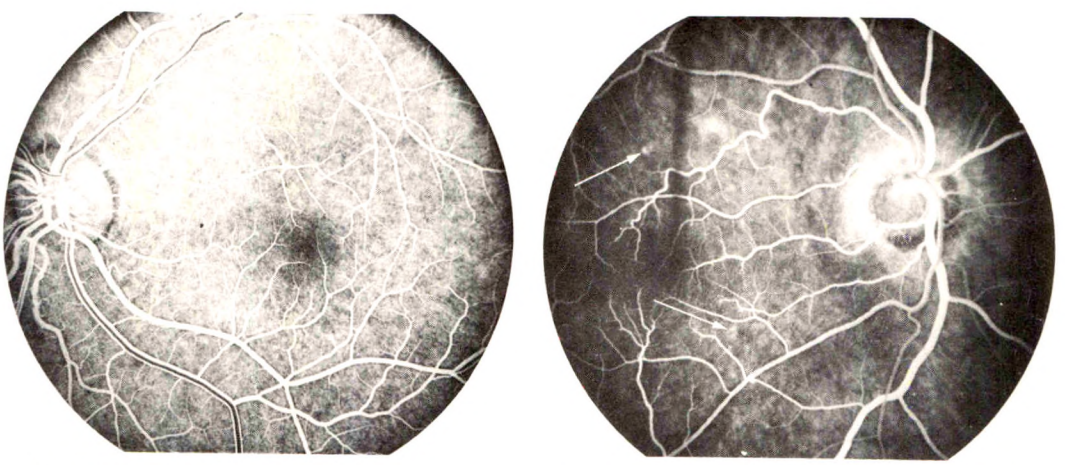

Fig. 5: (Hittner and associates). Fundus fluorescein angiography of affected family members. Left, Case III-7, Angiogram of patient with 6/6 (20/20) visual acuity (left eye). Note absence of capillary free macular area 19.7 seconds after dye injection. Right, Case III-2, Angiogram of patient with 6/60 (20/200) visual acuity (right eye). Note absence of capillary free macular area 24.9 seconds after dye injection and small hyperfluorescent spots marked by arrows.

rescein angiography did not reveal any abnormalities in these areas and instead showed small hyperfluorescent spots. The nature of the spots seen in the fundi or on fluorescein angiography is not known. Perhaps they are related to the retinal lipid deposits in aniridic patients previously reported.[21]

Electroretinography showed abnormally low signals in patients with visual acuity below 6/18 (20/60) on a macular basis, and abnormally high a:b-wave ratios or abnormally high signal amplitudes in many patients with visual acuity above 6/15 (20/50) or with visual acuity decreased secondary to glaucoma, cataract, corneal pannus, or optic nerve hypoplasia. These abnormalities, however, were not consistent enough to be useful diagnostically. The electro-oculograms and visual-evoked responses were likewise of no diagnostic assistance.

Several previous reports have dealt with the pathogenesis of aniridia, with the two most popular explanations as follows: (1) the failure of the development of nonvascular neurectodermal components of the eye, and (2) the failure of the development of the vascular components of the eye, attributed by others to mesodermal defects.[22] The suggestion has been made that the more common and severe form of autosomal dominant aniridia is the result of the failure of the development of the nonvascular neurectodermal components of the eye, whereas the less severe form of familial aniridia is the result of the failure of the development of vascular elements.[13] The present family, with preserved ocular function and several abnormalities clearly related to abnormal development of both nonvascular neurectoderm and vascular components, shows that autosomal dominant aniridia may be a consequence of several pathogenetic mechanisms, and thus a wide spectrum of expressivity is not unexpected.

Our family shows the importance of thorough examination of family members of all patients with iris hypoplasia, iris colobomas (typical and atypical), and aniridia. Aniridia must be considered even in cases of atypical corneal pannus where decreased visualization of the anterior chamber makes it difficult to determine iris thinning. Autosomal dominant aniridia is often characterized by highly variable expressivity and examination of family members is necessary to give accurate genetic counseling.

Addendum—A separate study has recently indicated probable linkage of this family's autosomal dominant aniridia to acid phophatase-1 on chromosome.

Summary

Of 39 members in a family with autosomal dominant aniridia with variable expressivity, 16 members, representing 50% (15 out of 30) of those at risk, were affected. Of these, ten of 16 (63%) had visual acuity of 6/12 (20/40) or better in at least one eye, and six of 16 (37%) had visual acuity between 6/15 (20/50) and 6/60 (20/200) in at least one eye. Affected patients had nystagmus (12, 75%), cataracts (nine, 56%), strabismus (15, 94%), amblyopia (six, 37%), corneal pannus (one, 6%), glaucoma (one, 6%), macular hypoplasia (five, 31%), and optic nerve hypoplasia (one, 6%). The good visual acuity in this family indicates that absence of iris tissue is not responsible for the decreased visual acuity usually associated with aniridia. The decreased visual acuity correlates instead with a decreased macular reflex and with a decreased electroretinogram amplitude. Affected family members have abnormal persistence of vessels in the macular region angiographically, and when sufficient iris tissue is present to be studied angiographically, there are abnormal vascular loops and leakage of dye at the pupillary border.

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EARLY IDENTIFICATION OF RETINAL ANGIOMAS IN A LARGE KINDRED WITH VON HIPPEL-LINDAU DISEASE

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von Hippel-Lindau disease is a multisystem disorder with widespread manifestations. The findings encompassed by this syndrome were first clarified by Lindau[1] in 1926. He established the relationship between the vascular tumors of the retina described by von Hippel[2] in 1904 and cerebellar cysts. He reported similarities in the histology of both lesions. An autosomal dominant mode of inheritance has been described.[3] Van der Hoeve[4] classified it with the phakomatoses. Cysts of the pancreas, kidneys, epididymis, liver, lung, adrenals, bone, omentum, and mesocolon[1,5-10] have been described in von Hippel-Lindau disease as well as an association with renal carcinoma, pheochromocytoma, and meningioma.[11-14] Several reviews of von Hippel-Lindau disease have been published.[15-17] The manifestations of the disease vary widely among individuals and kindreds. Some of its manifestations such as pancreatic cysts can be benign, whereas the involvement of the central nervous system, eye, and kidneys can be devastating.

The early identification of affected individuals has been shown to be of benefit in both genetic counseling and treatment. Ophthalmoscopic examination for the presence of retinal angiomas is an effective method of screening individuals at risk.[18]

We present herein the results of the prospective screening of a large kindred afflicted with von Hippel-Lindau disease and emphasize the incidence and appearance of early retinal angiomas with special reference to atypical fundus lesions.

SUBJECTS AND METHODS

We studied a large kindred of 221 members (Fig. 1), most of whom reside on the island of Oahu in Hawaii. Fifteen of the individuals had von Hippel-Lindau disease, and some had been treated. However, the entire kindred had never undergone a complete prospective evaluation. An attempt was made to contact every living member of the family. Histories were obtained from 182 members, and 155 were examined. Screening included physical examination, complete blood cell count, urinalysis, indirect ophthalmoscopy, and abdominal ultrasound. Indirect ophthalmoscopy was not attempted in those younger than 6 years of age. If indicated, the patients received more extensive examination such as excretory urograms, renal angiography, and vertebral angiography. Of the 155 members examined, 111 received a complete ophthalmologic examination including visual acuity, tonometry, slit-lamp anterior segment examination, and examination with indirect ophthalmoscopy. Fluorescein angiography was not done in all of those examined. In 22 of the members, routine examination of the retina showed suspicious lesions, and fluorescein angiography was performed.

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army.

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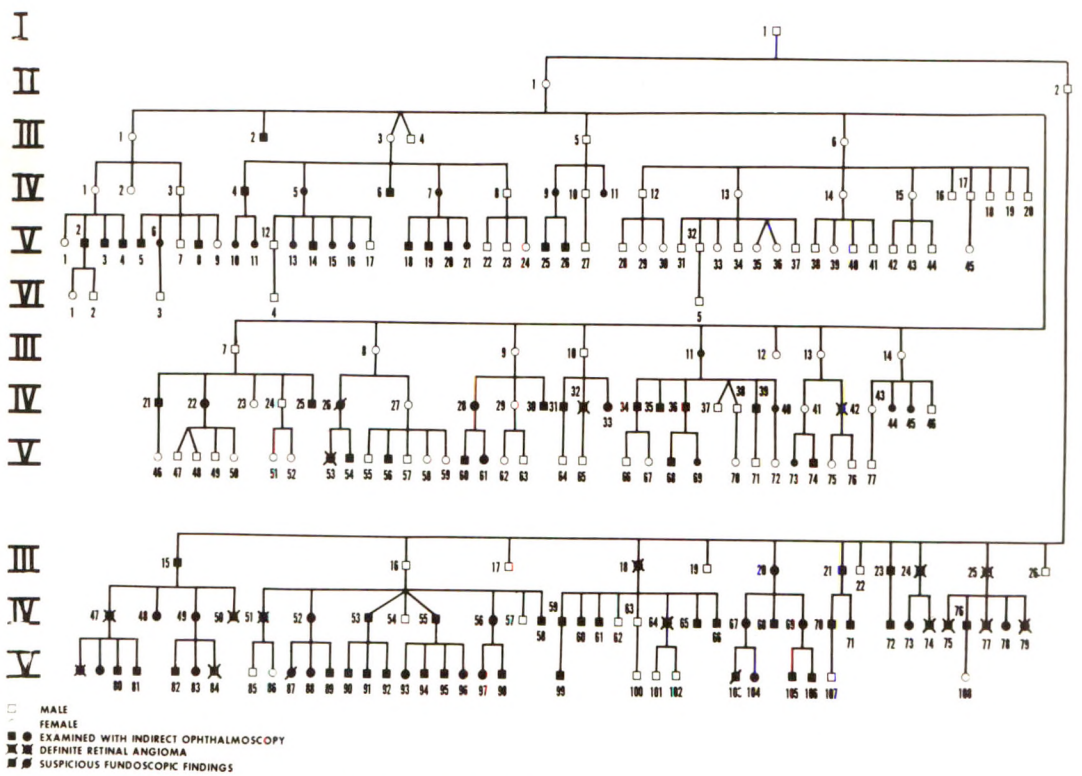

Fig. 1 (Salazar and Lamiell). Pedigree of entire kindred.

Serial examination of the eyes was not done. Those found to have retinal lesions were referred to civilian ophthalmologists.

Results

The screening program showed 27 additional cases of von Hippel-Lindau disease for a total of 42 individuals with von Hippel-Lindau disease. Of these 42 individuals, 15 had died and thus were not available for examination. In retrospect, it is likely that two of the 15 deceased individuals had retinal lesions. Of the 27 living affected members, three did not receive an ophthalmologic examination.

Of the 111 individuals who received ophthalmologic examinations, 17 were found to have either a definite angioma or a lesion indicative of one (Table 1). The positive findings could be classified into one of three groups: (1) classic angiomas, (2) atypical angiomas, and (3) suspicious ophthalmoscopic findings. There were 12 classic and four atypical angiomas, and there were three individuals whose ophthalmoscopic appearance was indicative of retinal angioma.

Group 1 lesions consisted of pink to red tumors (Figs. 2 and 3) located in the midperiphery with visible dilated feeder vessels and a variable amount of exudation. Group 2 lesions were usually pale gray in color (Fig. 4) and had no dilated feeder vessels or exudation, but fluorescein angiography or angioscopy confirmed their retinal vascular nature. Group 3 consisted of three individuals with lesions similar to those of Group 2, or lesions resembling diabetic microaneurism, but fluorescein angiography did

TABLE 1

SUMMARY OF AFFECTED CASES*

Pedigree No.	Age (yrs)	Group	Comment
IV-32	25	1	Renal carcinoma, renal cysts, spinal hemangioblastoma
III-18	54	1	Pancreatic cysts, pancreatic carcinoma, renal cysts, renal carcinoma
III-24	33	1	Spinal hemangioblastoma, renal cysts, renal carcinoma
IV-26	35	3	Pancreatic mass, splenomegaly
V-53	17	2	No systemic findings
IV-47	33	1	Cerebellar hemangioblastoma
IV-51	36	1	Pancreatic cyst, adenocarcinoma of ampulla of Vater, renal cysts, renal carcinoma
IV-74	16	2	Epididymal cyst
IV-75	22	1	Renal cyst, epididymal cyst, renal carcinoma
IV-77	19	1	Epididymal cyst
V-78	13	1	No systemic findings
III-25	35	1	Pancreatic cyst
IV-50	24	1	Spinal hemangioblastoma, renal cyst, renal carcinoma, epididymal cyst
IV-64	26	2	No systemic findings
V-84	11	3	No systemic findings
V-103	14	3	No systemic findings
IV-42	24	1	No systemic findings

*Cases afflicted with retinal angiomas. Age refers to the time of diagnosis of the retinal angioma.

not show a retinal vascular connection (Figs. 5 and 6).

There was no sex predilection. Only two of those members with retinal angiomas actually had ocular complaints. Indirect ophthalmoscopy led to the diagnosis of von Hippel-Lindau disease in 13 of the 42 affected members. All but one of the individuals were younger than age 40

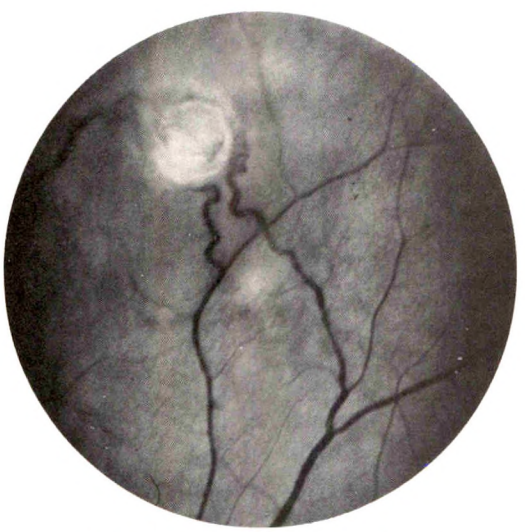

Fig. 2 (Salazar and Lamiell). Fundus picture of patient IV-51, representative for Group 1 lesions.

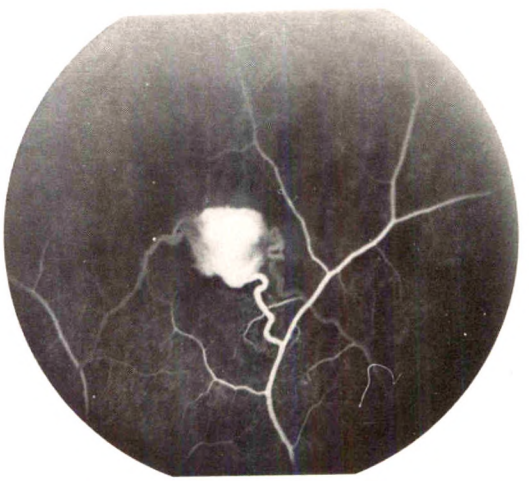

Fig. 3 (Salazar and Lamiell). Fluorescein angiogram of patient IV-51, representative for Group 1 lesions.

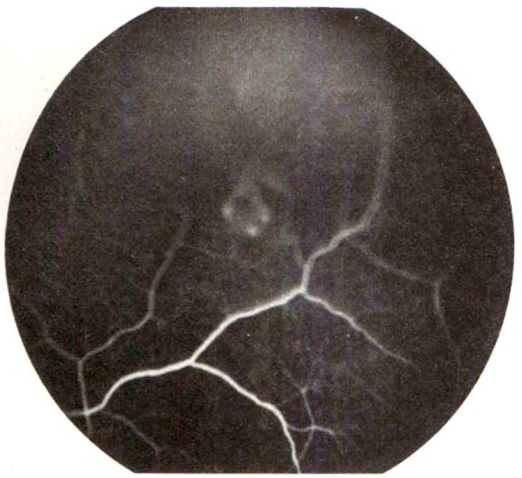

Fig. 4 (Salazar and Lamiell). Fluorescein angiogram of patient V-53, representative for Group 2 lesions.

Fig. 5 (Salazar and Lamiell). Fundus picture of patient IV-26.

years (Table 2). The average age at diagnosis of the entire group was 24 years; the average age at diagnosis was 27 years for Group 1, 18 years for Group 2, and 21 years for Group 3. The overall incidence of bilaterality was 29% (five of 17). Four cases were bilateral in Group 1, one in Group 2, and none in Group 3.

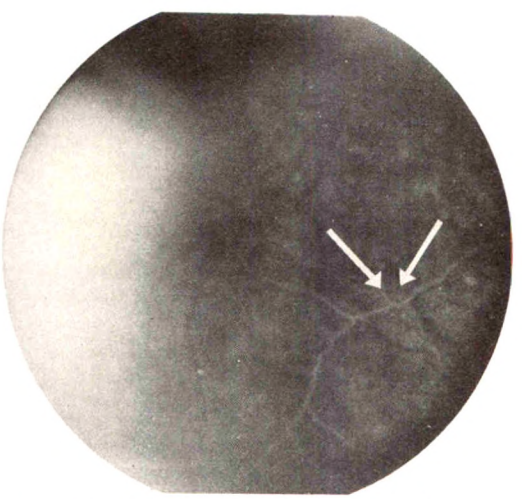

Fig. 6 (Salazar and Lamiell). Fluorescein angiogram of patient IV-26. Arrows show small dotlike lesions and tortuosity of retinal vein. Fluorescein angiogram shows those lesions to be avascular.

The incidence of definite retinal angiomas among those with von Hippel-Lindau disease was 38% (16 of 42). If the three cases from Group 3 are included, the incidence is 45% (19 of 42).

Discussion

The management of von Hippel-Lindau disease and its genetic counseling are facilitated by early diagnosis. Welch[19,20] emphasized the value of ophthalmologic screening and described some of the early manifestations of retinal angiomas. The classic thinking for many years was that in order to establish the presence of a retinal angioma the existence of a connection between the retinal circulation and the suspected

TABLE 2

Age distribution

Age Range (yrs)	No. of Patients
10-20	8
20-30	5
30-40	5
Over 40	1

lesion should be shown. Undoubtedly this is true in most patients who have ocular symptoms because it is usually these large lesions that have an exudative character. However, others[18,20] have noted that retinal angiomas may occur as a small red or pale gray nodule, with or without feeder vessels and with or without fluorescence on fluorescein angiography.[21] This could be explained by the pathogenesis of retinal angiomas. The most widely accepted theory of pathogenesis states that these lesions are of mesodermal origin[22] consisting of nests of endothelial cells with a variable amount of glial elements.[23] Cushing and Bailey[24] reported cases in which angiomas were noted to develop from what had previously appeared to be a normal retina. They also reported the evolution of a solitary retinal nodule into a classic retinal angioma.

In our study, the patients in Group 3 had lesions that probably belong in this category. Because accurate classification of these lesions at the time of initial examination was difficult, the diagnosis of retinal angioma was deferred. Two patients in this group are in their early teens and one is in the mid 30s. The older patient is the only one with systemic evidence of von Hippel-Lindau disease.

The average age of diagnosis in Group 2 is 18 years, and again only one has extraocular manifestations of von Hippel-Lindau disease. In Group 1 the average age at the time of diagnosis of the retinal lesions was 27 years, whereas all but three of this group had systemic manifestations of the disease (Table 3).

There seems to be a relationship between age, size of the retinal lesion, and systemic manifestations of von Hippel-Lindau disease. The time course that these lesions will follow cannot be accurately predicted. However, we believe that these lesions have a tendency to progress in a step-wise fashion from Group 3 to Group 2 to Group 1. Another possibility is that these lesions stabilize at an early stage and remain avascular. That none of these avascular nodules were found in any patient older than age 35 years in this study lessens this possibility. We believe these lesions represent early angiomas. Only careful follow-up of these lesions will definitely confirm or disprove this contention.

TABLE 3

ASSOCIATED SYSTEMIC FINDINGS

Group	Finding	No. of Cases
1	Pancreatic cysts	3
1	Renal carcinoma	6
1	Renal cysts	6
1	Spinal hemangioblastoma	3
1	Cerebellar hemangioblastoma	1
1	Epididymal cysts	3
1	Adenocarcinoma of ampulla of Vater	1
1	Pancreatic carcinoma	1
1	No systemic findings	3
2	Epididymal cyst	1
2	No systemic findings	3
3	Pancreatic mass	1
3	Splenomegaly	1
3	No systemic findings	2

SUMMARY

We studied prospectively a large kindred afflicted with von Hippel-Lindau disease. Of 111 members examined ophthalmoscopically, 14 definite retinal angiomas were found and three lesions were thought to be angiomas. The lesions found could be divided into the following three groups: (1) classic angiomas, (2) atypical angiomas, and (3) lesions indicative of early angiomas. A correlation between increasing age, systemic evidence of disease, and size and appearance of angiomas was found.

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THE CLINICAL AND MORPHOLOGIC CHARACTERISTICS OF KAPOSI'S SARCOMA OF THE CONJUNCTIVA

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In 1872, Kaposi[1] described the entity of multiple idiopathic hemorrhagic sarcoma, which has subsequently become known as Kaposi's sarcoma. This sarcoma usually originates in the skin and is characterized by blue-red or dark brown maculae or nodules on the lower extremities. It is a common neoplasm in Africa, south of the Sahara, but is rare elsewhere, occurring mainly in people of Central European, Jewish, or Mediterranean extraction. The disease occurs primarily in older age groups (over age 50 years) and is more common in men.[2–5]

Other neoplasms are associated with Kaposi's sarcoma, mainly lymphomas and leukemias.[6,7] Herpes virus[8] and immunologic incompetence[9] have been implicated as the cause. Kaposi's sarcoma appears to be of multicentric origin and is rarely metastatic.[10,11] The histogenesis of Kaposi's sarcoma is still controversial because of its varied histologic expression, but most are of the opinion that it originates from vasoformative mesenchymal cells.[12–16]

Involvement of the conjunctiva is rare.[17–20] We recently observed a case involving the palpebral conjunctiva.

CASE REPORT

A 77-year-old woman developed painful focal lesions on the soles of both feet in February 1974. Skin biopsy revealed "atypical proliferation of the vascular channels and spindle-shaped stromal cells with some focal hemosiderin deposition consistent with Kaposi's sarcoma." Results of examination for metastasis were normal and she received 3,000 rads in divided doses of radiation therapy to the lower extremities, which resulted in shrinkage of the lesions. In August 1975, she developed bilateral leg edema secondary to lymphedema. She was also noted to have lesions on her abdomen, arms, face, and right eyelid. A repeat of 500 rads of radiation was given to both legs, which resulted in decreased edema. The eyelid lesions progressed in size and bled intermittently.

An ophthalmic examination was performed in October 1975, at which time the right upper eyelid was involved with a fleshy, highly vascular mass (Fig. 1). The lesion extended from the right medial canthus to within 5 mm of the lateral canthus. Internally, the lesion appeared to be limited by the tarsus. Externally, despite vascular engorgement of

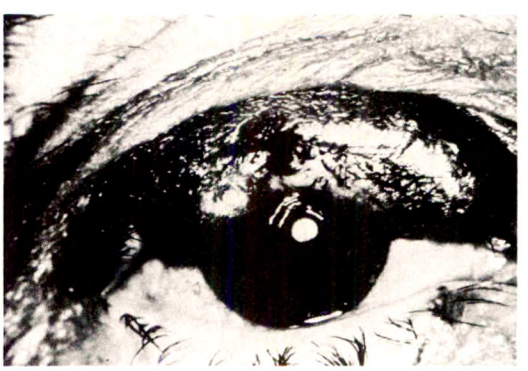

Fig. 1 (Weiter, Jakobiec, and Iwamoto). Appearance of Kaposi's sarcoma on right upper eyelid.

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the eyelid, the lesion appeared to stop at the mucocutaneous junction.

A biopsy specimen of the conjunctival tumor indicated Kaposi's sarcoma. Consultation was obtained with an ophthalmic plastic surgeon, who recommended radical removal of the right upper eyelid, but because of the patient's wishes and the possibility of later radiotherapy, a localized excision was performed in October 1975.

The lesion was limited macroscopically to the subconjunctival corium without invasion of the underlying tarsus or extension into the subdermal region of the eyelid. Microscopically, there appeared to be extension of neoplastic elements to the cut margins. Thirty-six months later, the eyelid was nicely healed with good functional and cosmetic results and no evidence of residual tumor or recurrence (Fig. 2).

Subsequent examination in September 1976 revealed involvement of the stomach by Kaposi's sarcoma and the patient has received systemic chemotherapy with 25 mg of methotrexate weekly.

Histopathologic findings—The conjunctival tumor was sectioned in two parts at the time of surgical excision. One part was fixed in formalin, embedded in paraffin, sectioned at 7μ and processed for light microscopy using hematoxylin and eosin, PAS, Fontana, reticulin, and trichrome stains. The other part was fixed in Karnovsky's solution, osmicated and embedded in Epon for transmission electron microscopic study.

Light microscopy—The lesion was variable in appearance. Superficial regions had multiple dilated vascular channels (Fig. 3) with prominent endothelial cells. A perivascular as well as a diffuse chronic inflammatory cell infiltrate was evident. The stroma appeared edematous and did not contain mature collagen bundles. The overlying conjunctiva underwent metaplasia to form a nonkeratinized squamous epithelium. Deeper parts of the tumor showed areas that were either angiomatous or fibroblastic in appearance. Occasionally these areas were intermingled (Fig. 4) The irregular fascicles of spindle-shaped cells had poorly defined cell outlines and the nuclei varied in size and tinctorial properties. In the more angiomatous areas, there were vascular lumina of varying sizes. In general, these lumina were surrounded by a single layer of prominent endothelial cells (Fig. 5). The prominent feature of these deeper lesions was the widespread extravasation of erythrocytes and deposition of hemosiderin. In the angiomatous areas, the proliferating endothelial cells created a nesting pattern in which groups of endothelial cells were outlined by the reticulin stain, whereas in the fibroblastic areas the reticulin stain outlined individual cells.

Electron microscopy—On electron microscopic examination using low power scanning magnification, erythrocytes were trapped in small clefts and pseudolumens. Under higher power, vascular differentiations were often complete, consisting of endothelial cells joined together by junctional complexes (Fig. 6). Such vascular channels, however,

Fig. 3 (Weiter, Jakobiec, and Iwamoto). Conjunctiva at top. Superficial regions show multiple dilated vascular channels. Erythrocytes and hemosiderin are present in the intercellular spaces (hematoxylin and eosin, ×100).

Fig. 2 (Weiter, Jakobiec, and Iwamoto). Appearance of eye after local excision of Kaposi's sarcoma.

Fig. 4 (Weiter, Jakobiec, and Iwamoto). Histologic section showing angioblastic component and spindle cell proliferation in contiguous regions (hematoxylin and eosin, ×200).

Fig. 5 (Weiter, Jakobiec, and Iwamoto). Histologic section of angiomatous region showing the typical hyperemic vascular slits. Most lumina are lined by endothelial cells, but some are surrounded also by fibroblasts. Extravasated erythrocytes are present outside of vascular lumina (hematoxylin and eosin, ×350).

were abnormal in that the endothelial cells usually lacked pericytes. Furthermore, the endothelial cells manifested abnormal phagocytic activity with lysosomes and hemosiderin granules within the cytoplasm. More often the vascular spaces were abortive (Fig. 7). Endothelial cells incompletely surrounded single erythrocytes or small collections of erythrocytes. Cells with pericytic features were often in contact with the erythrocytes because of gaps in the continuity of the endothelial cells. Both pericytes and the endothelial cells in such instances were apt to contain hemosiderin. The endothelial cells were identified by the formation of junctions, but these were inconstantly present and probably were the sites of extravasation of erythrocytes. The endothelial cells frequently displayed cytoplasmic filaments with fusiform densities. The pericytes, however, sometimes showed evidence of smooth muscle differentiation consisting of fine filaments with fusiform densities. Incomplete basement membranes surrounded the endothelial cells and pericytes where they abutted on the extracellular space, but where erythrocytes were in contact with the pericytes in the extravascular spaces the pericytes failed to display basement membrane formation.

Discussion

Kaposi's sarcoma is an interesting, but bizarre neoplasm, particularly with regard to its predilection for the skin and its distribution as to age, sex, race, and geography.[1–5] Although formerly considered rare, it has been seen with greater frequency.[2,4–7] Most lesions begin on the lower limbs, but as the disease progresses, almost every organ in the body may be affected. Kaposi's sarcoma causes death in only 10 to 20% of those affected with it.[10,11]

Involvement of this tumor in the area of the eye is uncommon, which accounts for lack of experience in the ophthalmic community with respect to its management. Because of its multicentric origin and tendency to progress, the usual therapy consists of irradiation or chemotherapy. This case is important because it shows the usefulness of surgical excision of isolated nodules in the region of the eye. The tendency for regression of incompletely excised Kaposi's sarcoma nodules in the conjunctiva has been previously reported by Mortada.[18] Furthermore, Howard, Jakobiec, and DeVoe[20] in a case report, noted greater edema in areas of conjunctivae possessing greater substantia propria and an apparent limitation of growth in the conjunctiva overlying the tarsus. These observations give greater flexibility to the ophthalmic surgeon in the management of these lesions, particularly when dealing with structures that do not lend themselves to the excision of a wide margin of tumor-free tissue.

There has been controversy as to the histogenesis of this neoplasm. Most pathologists today believe that this is a tumor of the vasoformative mesenchymal tissue. More specifically, Hashimoto and Lever[13] implicate pericytes and endothelial cells. The present study confirms this opinion. We were able to show the nesting pattern outlined by the reticulin stain as seen in proliferating endothelial cells and find the individual spindle cells surrounded by reticulin fibers in the fibroblastic areas.[21] On electron microscopic examination the spindle cells had features consistent with a pericyte, including basement membrane formation, either completely or incompletely surrounding the cells; scant cytoplasmic filaments with occasional fusiform densities char-

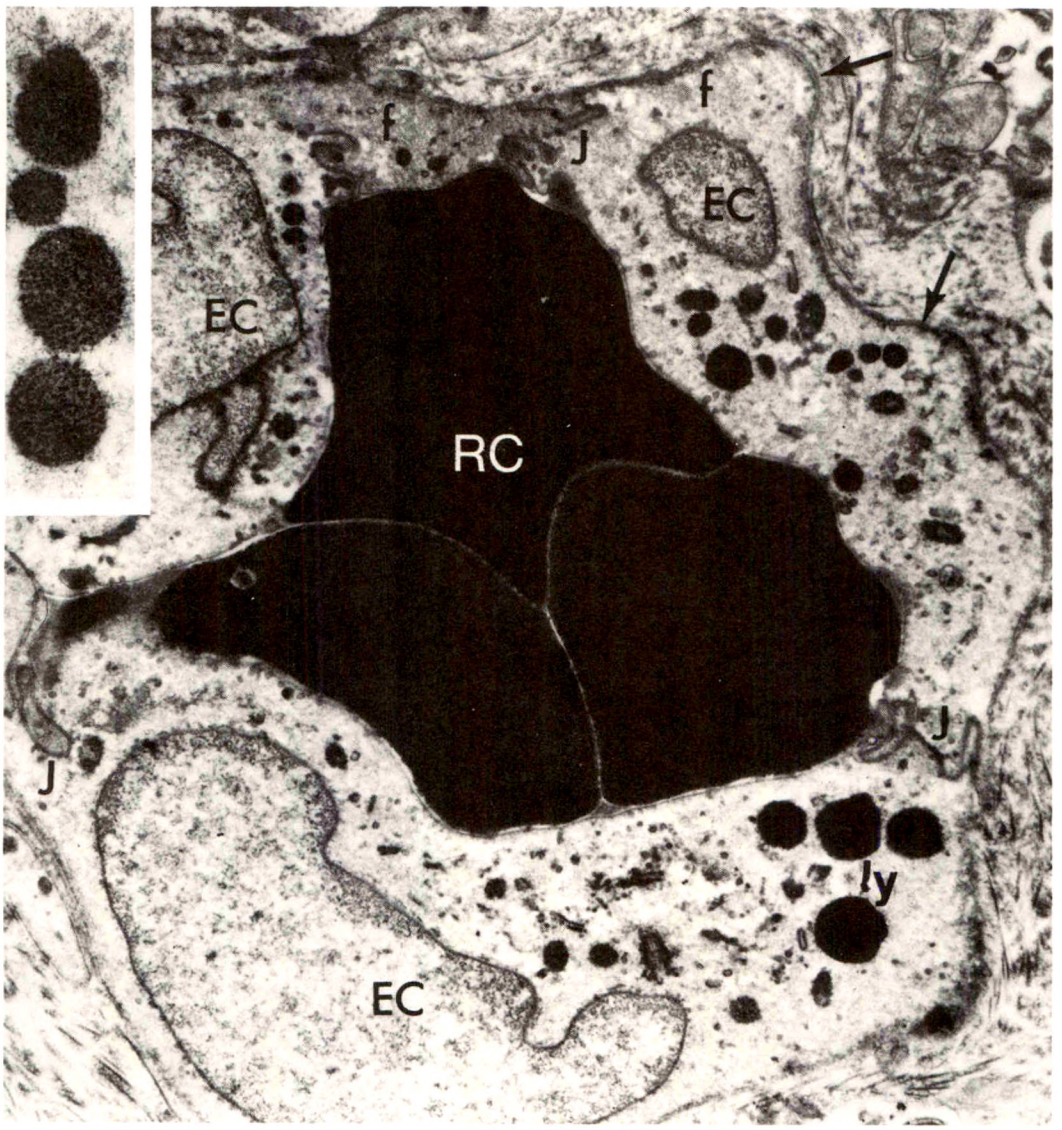

Fig. 6 (Weiter, Jakobiec, and Iwamoto). A group of tumor cells differentiated into a complete blood vessel. Several endothelial type cells (EC) with cytoplasmic filaments (f) are joined by tight junctions (J). They enclose a complete lumen with erythrocytes (RC) internally, and are surrounded by a basement membrane (arrows) externally. The whole structure thus closely resembles a normal blood capillary except for the presence of unusually many lysosomes (ly), which at higher magnification contain aggregates of ferritin particles (inset). Similar ferritin-containing lysosomes were also found in cutaneous lesions (13,15,16), and are probably derived from phagocytosed erythrocytes (13). (×12,700; inset, ×29,900).

acteristic of pericytic smooth muscle cells; moderate profiles of rough endoplasmic reticulum and Golgi lamellae; and scattered pinocytotic vesicles. Many of the spindle cells were actively engaged in phagocytosis and contained the spectra of activity including primary phagosomes containing erythrocytes, secondary lysosomes containing hemosiderin, and tertiary lysosomes or myelin figures.

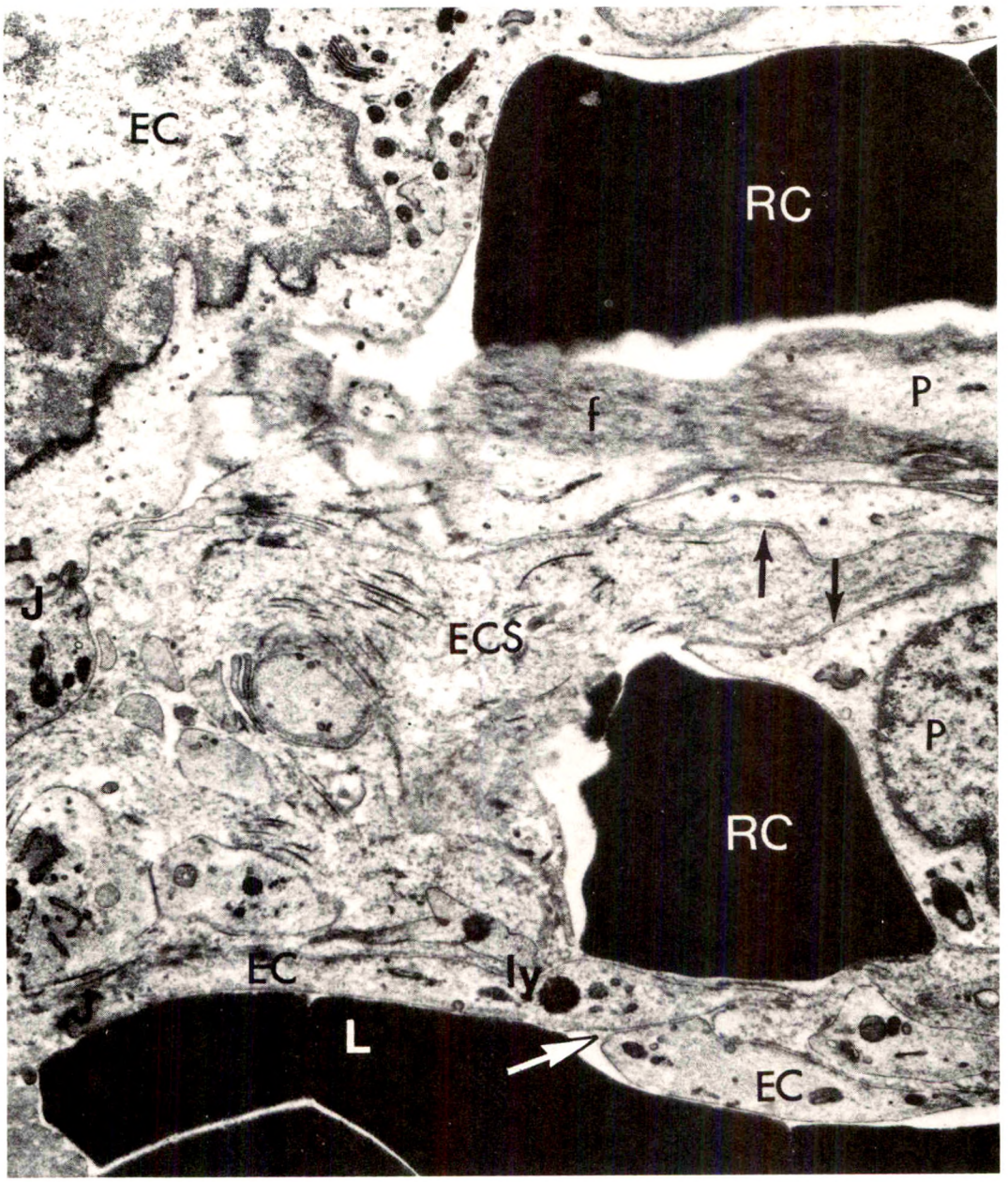

Fig. 7 (Weiter, Jakobiec, and Iwamoto). Another tumor area with extravasated erythrocytes. Endothelial type cells (EC) are sometimes not sealed by a tight junction but only loosely apposed (arrows). Probably as a result, erythrocytes (RC) are often found in the extracellular spaces (ECS). Pericytes (P) are commonly present around the endothelial type cells, and a few of them exhibit partial cytoplasmic filaments (f) with fusiformlike densities suggesting early smooth-muscle cell differentiation. L, lumen; J, tight junction (×24,700).

Our electron microscopic studies indicate that Kaposi's sarcoma is a tumor of vascular origin, rather than of lymphoreticular cells, histiocytes, or neurogenic cells. Some of the better formed vascular channels showed a completely lined endothelial tube with junctional complexes, but these vascular spaces were manifestly abnormal, owing to phagocytic activity with hemosiderin collection and the absence of pericytes. Other vascular channels were obviously abortive, being incompletely lined by endothelial cells focally displaying absence of junctional complexes. In such instances erythrocytes had extravasated into the extravascular space where they lay adjacent to either pericytes or the basal surface of the endothelial cells without the interposition of basement membrane material. The endothelial cells frequently exhibited cytoplasmic filaments. The pericytes were either ovoid or more elongated; in the latter case they were likely to possess cytoplasmic filaments with fusiform densities in keeping with incipient smooth muscle differentiation.

Although the cause of Kaposi's sarcoma is unknown, we may speculate that the primary mechanism is an uncoupling of the contact inhibition that the pericyte is postulated to exert on the natural tendency of endothelial cells to proliferate.[22] This concept would extrapolate to the findings in diabetic retinopathy. de Oliveira[23] suggested that retinal capillary pericytes are capable of migration and that endothelial proliferation occurs in vessels in which the pericytes are scarce or absent. Michaelson and associates[24] have shown that in diabetic retinopathy with hemorrhages and exudates, the phagocytes are on the inner aspect, closest to the retinal capillaries. They speculate that the exudate serves as a stimulus for pericyte migration, resulting in uncoupling of the endothelial cell proliferation. Bloodworth and Molitor[25] also observed that the reduction in capillary pericytes takes place chiefly in areas where microaneurysms, exudates, and hemorrhages are most abundant. Kaposi's sarcoma may be useful in contributing to an understanding of the mechanism of neovascularization.

Summary

A 77-year-old woman with known Kaposi's sarcoma of one year's duration developed nodular lesions of her right palpebral conjunctiva. Biopsy confirmed sarcomatous involvement and local resection was performed. Despite leaving residual tumor, there was complete regression of the eyelid tumor three years after the resection. Electron microscopic studies characterize this neoplasm as a proliferation of primitive endothelial cells and pericytes, the two cell lines that compose a capillary wall.

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Ophthalmic miniature

A man comes to you and tells you he is blind in one eye. Do you accept his statement? Not in the least. You proceed to test his eyesight with some infernal apparatus of colored glasses, and you find that he can see perfectly well with both eyes. Then you decide that he is not blind in one eye; that is to say, you reject his testimony in favor of facts of your own ascertaining.

R. Austin Freeman
The Eye of Osiris
1925

PUPILLARY DILATATION WITH SINGLE EYEDROP MYDRIATIC COMBINATIONS

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Parasympatholytic and sympathomimetic drugs administered topically are commonly used to obtain pupillary dilatation for ophthalmoscopy. Although either class of drug used alone will produce adequate mydriasis, experience and studies have shown that the use of both a sympathomimetic drug and a parasympatholytic drug produces maximal mydriasis that is resistant to intense light stimulation as in indirect ophthalmoscopy or fundus photography.[1,2] Drugs such as tropicamide (Mydriacyl), cyclopentolate HCl (Cyclogyl), and phenylephrine (Neo-Synephrine HCl) are used by many ophthalmologists before ophthalmoscopy. Usually two or three drops of each drug are instilled into each eye simultaneously or separately over a short period of time.

Systemic toxicity to these medications has been reported in all age groups; pediatric patients are particularly prone to these adverse effects.[3] The conjunctival sac retains only one fifth of one drop,[4] with the excess solution overflowing onto the cheek or drained through the nasolacrimal system.[5] Thus, systemic absorption of excess drug may occur. The dangers are increased when multiple drops of the drugs are instilled. Additionally, drugs combined in solution achieve higher intraocular concentrations after instillation of a single eyedrop than when instilled as drops of separate solutions within five minutes, because of dilution occurring with multiple drops.[5]

We initiated a controlled study comparing several combinations of two mydriatic agents to determine whether a single drop of any of these solutions could produce wide and sustained pupillary dilatation and thus diminish the risk of systemic toxicity with multiple instillations of mydriatic drugs. Wide pupillary dilatation without toxicity has been reported in neonates in whom a single drop combination of three drugs (cyclopentolate HCl, tropicamide, and phenylephrine) was used, and it was greater than when each drug was used alone.[2] In the present study, in adults we used a single eyedrop combination of only two drugs, a mixture of a sympathomimetic agent, phenylephrine, and a parasympathomimetic agent, tropicamide or cyclopentolate HCl. Additionally, we studied the effect of using an anesthetic (proparacaine) administered topically before the instillation of the single eyedrop mydriatic combination.

SUBJECTS AND METHODS

The patients included in this study ranged in age from 16 to 84 years, with a mean of 54 years and median of 56 years. There were 56 males and 24 females. Corneal diameters ranged from 10.0 to 12.0 mm, with a mean and median of 11.5 mm. Thirty-seven patients had blue irides, 12 had hazel irides, and 31 had brown irides.

Sterile solutions in final concentrations of cyclopentolate HCl 0.5% with phenylephrine 2.5% (solution A), tropicamide 0.5% with phenylephrine 2.5% (solution B), and tropicamide 1.0% with phenyl-

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ephrine 2.5% (solution C) were prepared here. The mydriatic effect of these combination eyedrops was studied in four groups of 20 patients. The groups consisted of adult patients with no anterior segment disease seen consecutively at our clinic.

Patients in the first group received one drop of proparacaine 0.5% in each eye. After one minute, the closed eyelids were gently compressed with a tissue to remove possible excess fluid in the cul-de-sac, and one drop of solution A was instilled in one eye followed by one drop of solution B in the other eye. The second group of patients received drops of the same solutions, A and B, but without prior drops of proparacaine 0.5%. Solutions B and C were compared in the third and fourth groups, with and without antecedent proparacaine drops. The first ten patients in each group received one mydriatic combination eyedrop in the right eye followed by the other combination in the left eye. To standardize the administration of drops, the last ten patients in each group received the same eyedrops in reverse order; that is, the second combination was instilled in the right eye, and the first in the left eye.

The mydriatic combination eyedrops were administered in a double-masked manner: neither the patient nor the person administering the eyedrops knew which solution was given. However, both knew whether a drop of the anesthetic was instilled first.

The eyedrops were instilled into the inferior cul-de-sac of each eye, which had been pouched by pinching the lower eyelid while the patient looked up. The patient was then asked to look down and the lower eyelid was allowed to come in contact with the globe, enclosing the administered solution in a kind of conjunctival pocket. The patient was asked to close his eyes gently and not blink or squeeze the eyelids for one minute, thereby decreasing the outflow of solution onto the eyelids. This method of instillation was used to increase the contact time between the solution and the cornea.[6]

Each patient's corneal diameters were recorded, and pupillary diameters and reaction to the bright light of an indirect ophthalmoscope were measured 30, 45, and 60 minutes after instillation. The pupillary horizontal diameter was measured to the nearest 0.5 mm by using a millimeter rule and a loupe (×2.5) for magnification. This method of measurement was sufficiently accurate for our clinical purpose of determining whether the mydriatic combinations could provide ample and sustained pupillary dilatation for a thorough ophthalmoscopic examination.

Results

In the patients in whom solutions A (cyclopentolate HCl 0.5% with phenylephrine 2.5%) and B (tropicamide 0.5% with phenylephrine 2.5%) were compared, no difference was found in the pupillary dilatation obtained with either drop, with or without the use of proparacaine ($P < .05$) (Table 1). The dilatation obtained with both solutions was greater when preceded by the instillation of proparacaine than when no proparacaine was used ($P < .05$) (Figs. 1 and 2).

In those patients in whom solutions B (tropicamide 0.5% with phenylephrine 2.5%) and C (tropicamide 1.0% with phenylephrine 2.5%) were compared, no difference was found in the pupillary dilatation obtained, with or without proparacaine ($P < .05$) (Table 2). The dilatation obtained with solution C was somewhat greater with previous instillation of proparacaine, although the difference was not statistically significant (Fig. 3). The pupillary dilatation achieved with solution B and previously instilled proparacaine was significantly greater than without proparacaine at 60 minutes ($P < .05$),

TABLE 1

PUPILLARY DILATATION (MM) AFTER OCULAR INSTILLATION OF MYDRIATIC COMBINATION EYEDROPS CYCLOPENTOLATE HCL 0.5% WITH PHENYLEPHRINE 2.5% (SOLUTION A) AND TROPICAMIDE 0.5% WITH PHENYLEPHRINE 2.5% (SOLUTION B)

Minutes After Instillation	Solution A				Solution B			
	Without Proparacaine 0.5%		With Proparacaine 0.5%		Without Proparacaine 0.5%		With Proparacaine 0.5%	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
30	6.6	5.0-8.0	7.4	6.0-9.0	6.9	5.0-8.0	7.5	5.5-9.0
45	7.1	6.0-8.5	7.9	6.0-9.5	7.2	6.0-8.5	7.9	6.5-9.5
60	7.2	6.0-8.5	8.1	6.5-9.5	7.2	6.0-8.5	8.0	6.5-9.5

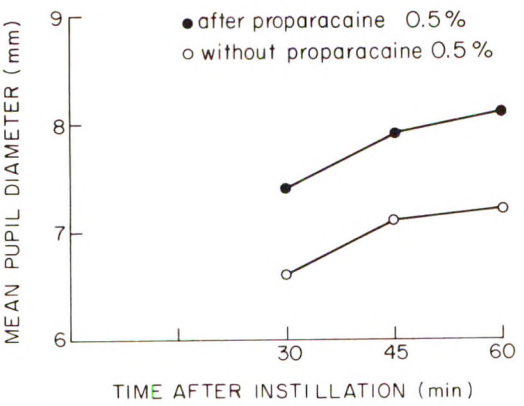

Fig. 1 (Apt and Henrick). Mean pupillary diameter obtained after instillation of one drop of cyclopentolate HCl 0.5% with phenylephrine 2.5%, with and without prior instillation of one drop of proparacaine 0.5%.

but not at the other observed times. Analyzing the pupillary dilatation of all eyes in which solution B was instilled showed that prior instillation of proparacine resulted in significantly greater dilatation at all observed times ($P < .05$) (Fig. 2).

The greatest pupillary dilatation occurred at 60 minutes for all solutions except solution B without proparacaine; maximum dilatation for this last combination was at 45 minutes ($P < .05$). We calculated the ratios of the patients' pupillary to corneal diameters. Statistical analysis of these ratios was similar to that of the pupillary diameters alone and was not used further.

All patients who did not receive proparacaine 0.5% eyedrops before the mydriatic combination drops complained of stinging on instillation of the eyedrops. These patients showed their discomfort by lacrimation and blinking or squeezing of the eyelids.

Pupillary dilatation was sustained long enough in all patients to perform a thorough indirect ophthalmoscopic examination 60 minutes after instillation of the mydriatic combination eyedrops. Essentially no pupillary constriction to even prolonged bright illumination was encountered.

Pupils of patients younger than age 55 years dilated better than those of the older patients ($P < .05$) (Fig. 4). Patients' sex made no difference in the response to the mydriatics ($P < .05$). Iris color also did not affect the amount of dilatation obtained ($P < .05$).

Discussion

No significant difference was found in the pupillary dilating effect of the three mydriatic combination solutions tested:

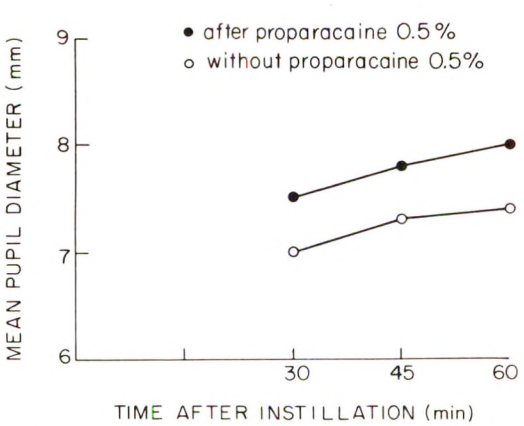

Fig. 2 (Apt and Henrick). Mean pupillary diameter obtained after instillation of one drop of tropicamide 0.5% with phenylephrine 2.5%, with and without prior instillation of one drop of proparacaine 0.5%.

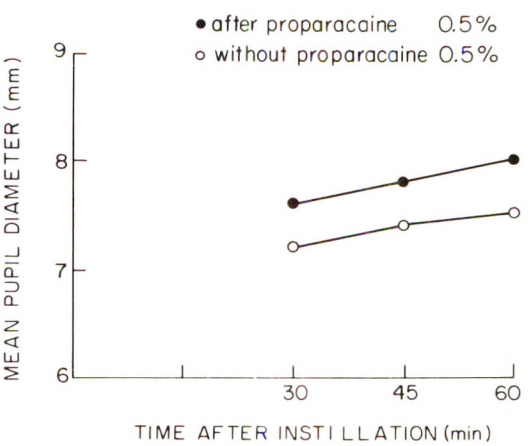

Fig. 3 (Apt. and Henrick). Mean pupillary diameter obtained after instillation of one drop of tropicamide 1.0% with phenylephrine 2.5% with and without prior instillation of one drop of proparacaine 0.5%.

TABLE 2

PUPILLARY DILATATION (MM) AFTER OCULAR INSTILLATION OF MYDRIATIC COMBINATION EYEDROPS TROPICAMIDE 0.5% WITH PHENYLEPHRINE 2.5% (SOLUTION B) AND TROPICAMIDE 1.0% WITH PHENYLEPHRINE 2.5% (SOLUTION C)

	Solution B				Solution C			
	Without Proparacaine 0.5%		With Proparacaine 0.5%		Without Proparacaine 0.5%		With Proparacaine 0.5%	
Minutes After Instillation	Mean	Range	Mean	Range	Mean	Range	Mean	Range
30	7.2	5.5-9.0	7.5	5.5-8.5	7.2	5.0-8.0	7.6	5.5-8.5
45	7.4	5.5-9.0	7.8	6.0-9.0	7.4	5.5-9.0	7.8	5.5-9.0
60	7.5	6.0-9.0	8.1	6.0-9.0	7.5	5.5-9.0	8.0	6.0-8.5

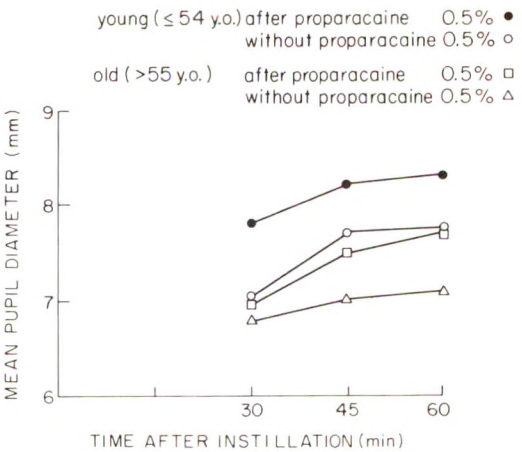

Fig. 4 (Apt and Henrick). Effect of age on pupillary diameter obtained after instillation of one drop of the mydriatic solutions tested with and without prior instillation of one drop of proparacaine 0.5%.

cyclopentolate HCl 0.5% with phenylephrine 2.5% (solution A), tropicamide 0.5% with phenylephrine 2.5% (solution B), and tropicamide 1.0% with phenylephrine 2.5% (solution C). However, a significant increase in pupillary dilatation was obtained when the mydriatic solutions A and B were preceded by the instillation of one drop of proparacaine 0.5%.

Although the data suggest that greater pupillary diameter was obtained by solution C preceded by proparacaine than by the combination mydriatic alone, statistical analysis proved the difference was not significant. The implied improved absorption of the combination mydriatic drug when preceded by the anesthetic can be explained by two mechanisms. First, proparacaine alters the corneal epithelium[7] and thus permits increased transcorneal absorption of the medication. Second, proparacaine, by eliminating the stinging sensation produced by the mydriatic combination eyedrop, diminishes the amount of tearing and blinking and thereby decreases the dilution and outflow of the mydriatic drugs. Intact corneal epithelium is the greatest barrier to drug penetration, with ionized drugs having the greatest difficulty crossing the lipid cell membranes.[8,9] Tropicamide (in solutions B and C), unlike cyclopentolate HCl (in solution A), is mostly nonionized at physiologic pH and can be expected to penetrate a cornea with intact epithelium more easily than cyclopentolate HCl.[10] Epithelium damaged by proparacaine thus allows improved ocular penetration of cyclopentolate HCl, but affects the penetration of tropicamide less. Phenylephrine, which also alters corneal epithelium,[11] could additionally improve the absorption of all the mydriatic drug combinations tested.

Pupils of younger patients dilated better than those of older patients, though sex of the patient made no difference. Contrary to previous experience that lightly pigmented irides dilate more than darkly pigmented irides,[12] iris color was not a factor in the amount of pupillary dilatation obtained with the three mydriatic combination eyedrops used in this study. Several investigators reporting on the mydriatic effect of tropicamide also found iris color was not a factor.[13,14]

Our study shows that wide pupillary dilatation and resistance to the bright and prolonged light used during indirect ophthalmoscopy can be obtained in adult patients within 60 minutes after using only one drop of any of the three mydriatic combination solutions tested. Further dilatation is obtained by prior instillation of one drop of proparacaine 0.5%. The low dose of mydriatic drugs thus administered assures a small risk of systemic toxicity. The results are especially important for infants and children, who have an increased potential for systemic toxicity from drugs instilled into the eye.

Summary

We studied the mydriatic effect of three solutions containing a combination of two mydriatic drugs in 80 adult patients. The solutions tested were cyclopentolate HCl 0.5% with phenylephrine 2.5%, tro-

picamide 0.5% with phenylephrine 2.5%, and tropicamide 1.0% with phenylephrine 2.5%. We evaluated the effect of prior instillation of proparacaine 0.5% eyedrops.

All three mydriatic combination solutions evaluated produced pupillary dilatation of about 7 mm within 60 minutes. Additional pupillary dilatation of 1 mm occurred when proparacaine was instilled before the mydriatic combination eyedrop. Mydriasis was resistant to bright light during indirect ophthalmoscopy in all patients. Pupils of younger patients dilated better than those of older patients, but sex and iris color were not factors in the amount of pupillary dilatation obtained.

Wide and sustained pupillary dilatation can be obtained for satisfactory indirect ophthalmoscopy by the instillation of one drop of proparacaine solution followed by a single drop of any of the three mydriatic combination solutions evaluated. By eliminating the need for multiple instillations of drugs, the use of a single eyedrop mydriatic combination is convenient in terms of time saved and also lessens the chance of systemic drug toxicity.

Acknowledgments

Stephanie Foote, Ph.D., assisted with the statistical analysis of the data, and John Y. Masuda, M.S., prepared the sterile eyedrop solutions.

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CHLORAL HYDRATE SEDATION AS A SUBSTITUTE FOR EXAMINATION UNDER ANESTHESIA IN PEDIATRIC OPHTHALMOLOGY

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The ocular examination of infants and young children is often complicated by poor patient cooperation. Retinoscopy, ophthalmoscopy, echography, slit-lamp biomicroscopy, keratometry, fundus photography, electroretinography, gonioscopy, and tonometry may be variably unsatisfactory or impossible. Before we used chloral hydrate as an outpatient sedative, general anesthesia was often necessary to perform these procedures. In pediatric patients who require scleral indentation, except for patients with retinoblastoma, chloral hydrate has all but eliminated the need for examination under general anesthesia (Figs. 1 and 2). Corneal sutures have even been removed and replaced with chloral hydrate and topical anesthesia.

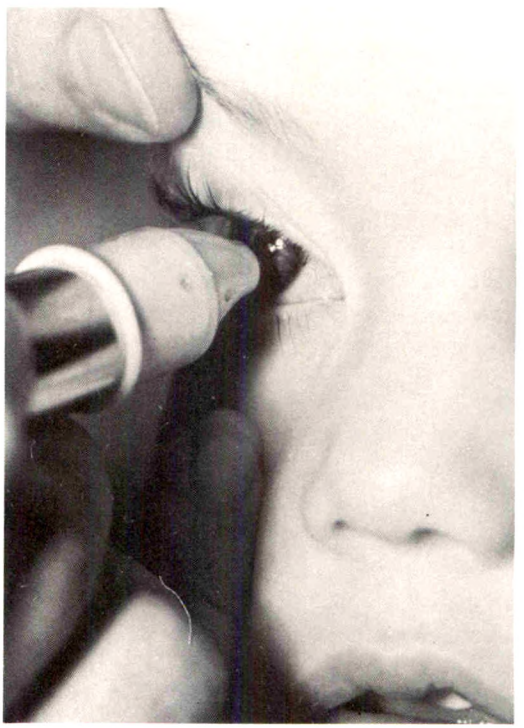

Fig. 1 (Judisch, Anderson, and Bell). Indirect ophthalmoscopy after chloral hydrate sedation. The eyelid speculum was inserted after topical anesthesia.

METHODS

Administration procedure—For infants and small children, the appropriate dose is drawn into a needleless syringe. The dose is deposited in suitable portions (not squirted, to avoid aspiration) into the side of the mouth. Parents may assist by holding the patient and retroflexing the head slightly to encourage swallowing. Gentle extremity restraint, temporary closing of the nostrils or stroking the anterior neck surface, or both, to encourage swallowing facilitate ingestion. An ounce or two of juice or formula reduces the aftertaste. Older children can drink the syrup with or without a few ounces of clear juice dilutant.

The protocol for chloral hydrate sedation includes the following:

1. With a normal, healthy, full-term infant 4 weeks of age or older, use 100 mg/kg of body weight to a maximum dose of 3.0 g.

2. If the baby is premature or unhealthy (respiratory, cardiovascular, or azotemic renal disease), less than 4 weeks of age or less than 4 kg, use 50 mg/kg of body weight. Mental re-

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Fig. 2 (Judisch, Anderson, and Bell). Mackay-Marg tonometry after chloral hydrate sedation and topical anesthesia.

tardation or cerebral palsy, or both, are not contraindications to full dosage.

3. If after 30 minutes there has been no response, one half the original dose in both situations 1 and 2 may be repeated.

After the medication is given the patient is examined. The maximum soporific effect is usually reached in 30 to 60 minutes. Continuous observation by a nurse or some other comparably experienced person is important while the patient is affected by the drug. Excitement or delirium, or both, may occur during induction or awakening. Parents are advised of this possibility and reassured that these reactions, which last anywhere from a few minutes to as long as several hours, are temporary. As drowsiness develops, the patient is placed on a side with the head slightly retroflexed to ensure an adequate airway and to prevent aspiration in the event of regurgitation.

As chloral hydrate is a gastric irritant, vomiting (seldom more than one episode) is not uncommon. However, enough drug is usually absorbed to achieve the desired effect. With or without vomiting, one half of the original dose may be repeated as necessary to obtain adequate sedation.

Patients are not discharged for at least 1½ hours after the chloral hydrate is given, or until they are easily aroused by noxious stimuli such as squeezing the heel, or sternal pressure. Patients should take nothing by mouth until fully awake. Feeding begins with small quantities of clear liquids, with the diet gradually increased as tolerated. In order to minimize vomiting, fluids only are suggested.

Pharmacology—Chloral hydrate is the oldest of the hypnotic drugs. It is a crystalline substance that is readily soluble in either oil or water. It is rapidly absorbed from all mucosal surfaces, which probably explains why patients who regurgitate usually still achieve the desired sedative effect. Once absorbed, most of the drug is rapidly reduced to trichloroethanol, which leaves the bloodstream slowly, and which may be responsible for the hypnotic effect. In recommended therapeutic doses, chloral hydrate produces a nonspecific reversible cerebral hemisphere depression to the level of sleep without significant alterations in respiration, blood pressure, or heart rate. The drug has little analgesic effect; pain may provoke excitement or delirium.[1,2]

Toxicity, side effects, and dosage—Acute chloral hydrate poisoning resembles barbituate intoxication; the patients show pinpoint pupils, coma, bradypnea, and hypotension. Death usually results from respiratory center depression. Maintaining an adequate airway and respiration are the primary concerns. Liver and renal damage may ensue if the patient survives.

Reports of chloral hydrate toxicity are scarce. The toxic dose given orally of chloral hydrate for adults is 10 g.[1] However, death has been reported from as little as 4 g and survival after ingesting as much as 30 g. Gastric necrosis has been observed in three suicidal adults who consumed from 18 to 150 g of chloral hydrate.[3]

No specific statements regarding toxic levels in infants or children were found.

A 3-year-old girl who survived an accidental dose of 7.5 g without sequelae has been described.[4] A 28-month-old boy was given 120 mg/kg of body weight by his father to "keep him quiet and help him get to sleep." The child developed a cardiac arrhythmia from which he completely recovered without treatment in 1½ hours.[5] Cardiorespiratory arrest, with complete recovery has been described in one patient secondary to aspirating a therapeutic dose of chloral hydrate.[6] As the drug is irritating to all mucus membranes, avoiding aspiration is important to prevent laryngospasm.

We have sedated more than 300 pediatric ophthalmology outpatients during the last three years according to the protocol explained previously. Transient vomiting (approximately 15% of the patients), excitement, or delirium (less than 5% of the patients, rarely requiring restraint or other special attention), were the only side effects. Complications were rare and mild. Bradypnea developed in one infant who did not become cyanotic or require respiratory support and recovered in less than three hours. One baby less than 1 month old required head retroflection for several minutes to maintain a patent airway.

Before using chloral hydration in the Ophthalmology Department, more than 200 pediatric patients were sedated by physicians in the Department of Pediatrics at the University of Iowa Hospitals and Clinics with this dosage, usually for computed axial tomography scans. The experience with these patients was essentially the same.

Recommended chloral hydrate dosages for children include 50 to 100 mg/kg of body weight,[7] 75 mg/kg of body weight,[8] and 50 mg/kg of body weight per 24 hours.[9] Although our schedule proposes doses larger than most, our experience with more than 500 patients reassures us as to the safety of the protocol.

Insufficient sedation was obtained in less than 1 to 2% of patients. Emesis of the administered drug was believed to be the cause of failure in most of these patients. One patient inadequately sedated by the protocol, who did not vomit, had satisfactory uncomplicated sedation with an additional dose of 15 mg/kg of body weight.

Irregular intraocular pressure measurements during general anesthesia complicate the diagnosis and management of congenital glaucoma. Recently, we began doing Mackay-Marg tonometry on clinically nonglaucomatous patients sedated with chloral hydrate. In 17 eyes, the readings ranged from 11 to 17 mm Hg; seven had pressures of 16 mm Hg.

There is no pharmacologic evidence that therapeutic doses of chloral hydrate affect the autonomic nervous system, aqueous production, outflow facility, or muscle tone. Thus, chloral hydrate sedation apparently does not alter the intraocular pressure.

Discussion

Chloral hydrate as a pediatric or pediatric-ophthalmologic sedative is not new,[10] yet it seems to be seldom used by most ophthalmologists. Many of the patients were seen here because of the inability of the referring doctor to examine adequately an uncooperative child or because of failure to recognize disorders that would have been diagnosed had a complete examination been possible.

General anesthesia is expensive, occasionally difficult to obtain, time-consuming, and probably a greater risk than chloral hydrate. The value of being able to examine a child completely on the initial outpatient visit is considerable, both economically and emotionally. Chloral hydrate given orally, a drug with a wide margin of safety in recommended doses, can be used in the office or clinic. It may also permit the accurate measurement of

intraocular pressures in patients with congenital or infantile glaucoma.

Summary

We examined more than 300 children as outpatients with orally administered chloral hydrate sedation during the past three years; 175 of them have been examined in the last year. Without chloral hydrate sedation, examination under anesthesia would have been necessary or the results would have been less than satisfactory. Orally administered chloral hydrate has a wide margin of safety and is most appropriate for office or clinic use. It may also allow accurate measurement of the intraocular pressure in infantile glaucoma.

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OCULAR PENETRATION OF CEFAZOLIN IN HUMANS AND RABBITS AFTER SUBCONJUNCTIVAL INJECTION

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Cefazolin sodium is a parenterally administered semi-synthetic cephalosporin with a broad spectrum of bactericidal activity. It produces high blood levels after parenteral administration,[1] is 85% protein bound,[2] has less cross-reactivity with penicillin derivatives than cephaloridine,[3-4] is excreted via glomerular filtration,[2] and has relatively few adverse effects.[5] As a result of these characteristics it may be a useful prophylactic and therapeutic drug in ophthalmology.

Abel, Kier, and Guckian[6] showed bactericidal aqueous levels in rabbits after subconjunctival administration of 25 mg of cefazolin from 15 minutes to more than three hours after injection. In another study, single intravenous doses of up to 1 g of cefazolin failed to produce therapeutic aqueous levels in five patients undergoing cataract extraction despite high serum levels.[7]

We determined the clinical potential of cefazolin by assaying aqueous samples for levels of aqueous penetration of cefazolin in man and rabbits after subconjunctival injection.

MATERIAL AND METHODS

Clinical studies—After instilling two drops of 0.5% proparacaine in the eye, 50 mg (0.15 ml) of cefazolin was injected subconjunctivally 3 mm inferior to the corneoscleral limbus in 11 patients undergoing routine intracapsular cataract extraction. A limbal-based conjunctival flap was reflected and a partial penetrating limbal incision was made. A 27-gauge needle mounted on a tuberculin syringe was then inserted through the clean, dry groove into the anterior chamber and 0.2 ml of aqueous humor was aspirated. The interval from injection to aspiration was noted. The sample was frozen at −20°C, and cataract extraction proceeded in the usual fashion.

Antibiotic assay was performed using the agar well diffusion method.[8] This method has the advantages of requiring small amounts (less than 10 μl) of sample for assay and is easily reproducible. Wells were punched on a seeded agar plate and a standard curve was constructed using zonal measurements of known concentrations of cefazolin with *Bacillus subtilis* as the indicator organism. The diameters of the zones of the unknown aqueous samples were measured and the concentrations were determined from the standard curve. All determinations (standards and unknowns) were done in triplicate.

Animal studies—Twenty Australian white rabbits, weighing approximately 3 kg, were sedated with 150 mg of ketamine administered intramuscularly. After instillation of two drops of 0.5% proparacaine, 22.5 mg (0.1 ml) of cefazolin was injected subconjunctivally 2 mm from the corneoscleral limbus in the superior nasal quadrant. The animals were killed at varying intervals with intracardiac pentobarbital (Nembutal) and 0.2 ml of aqueous was aspirated from the anterior chamber with a 27-gauge needle mounted on a tuberculin syringe. The samples were immediately frozen at −20°C.

Bioassay was done on a cylinder-plate

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system using *B. subtilis* as the indicator organism. The samples and standards were diluted with 0.1M, phosphate buffer (pH 6.0). Each sample was assayed on one to three plates depending on available sample volume.

Results

Clinical studies—The concentrations of cefazolin found in the aqueous within 30 minutes of injection are listed in Table 1. Aqueous penetration first appeared seven minutes after subconjunctival injection, was regularly present after 16 minutes, and increased in concentration up to 30 minutes after administration.

Although there were few complaints of pain, injection consistently produced chemosis with an occasional hemorrhagic component at the site. This cleared with no sequelae.

Animal studies—The Figure shows the aqueous levels of cefazolin after subconjunctival injection in rabbits. Twenty minutes after injection the average level was 8.2 μg/ml. The concentration gradually increased until an average level of 35.9 μg/ml was present two hours after injection. Thereafter, aqueous levels gradually declined but detectable levels were still present after eight hours in all samples.

TABLE 1

CONCENTRATION OF CEFAZOLIN IN HUMANS AFTER INJECTION OF 50 MG SUBCONJUNCTIVALLY

Sample No.	Time After Administration (min)	Concentration (μg/ml)
1	5	0
2	7	0
3	7	22
4	10	0
5	16	8
6	16	8
7	17	8
8	18	17
9	18	17
10	25	36
11	30	80

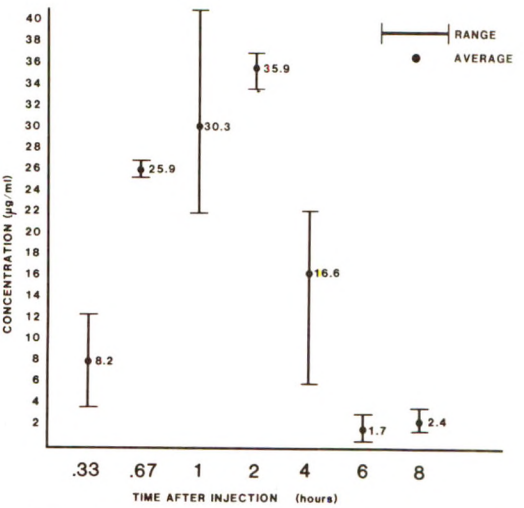

Figure (Saunders and McPherson). Concentration of cefazolin in rabbits after 22.5-mg subconjunctival injection.

Discussion

We use subconjunctival antibiotics prophylactically during all intraocular surgery and are constantly seeking alternatives for drug-allergic patients. Cefazolin appears to be an acceptable agent. Forster[9] indicated that *Staphylococcus epidermidis*, *S. aureus*, *Streptococcus* species, *Propionbacterium acnes*, *Proteus* species, *Pseudomonas*, and *Haemophilus influenzae* are now the most common causes of culture proven bacterial endophthalmitis.

Table 2 shows cefazolin's in vitro activity against these and other pathogens. Cefazolin is highly effective against *S. epidermidis*, penicillin sensitive and resistant *S. aureus*, *St. pyogenes*, and *St. pneumoniae*; moderately effective against *Escherichia coli*, *H. influenzae*, *Klebsiella* and *Proteus mirabilis;* ineffective against *Enterococcus*, indole-positive *Proteus* and *Pseudomonas*. The level of antibiotic detected in our determinations in the aqueous in humans and rabbits greatly exceeded the minimum inhibition concentration for those bacteria commonly causing endophthalmitis with the exception of *Pseudomonas*. This indicates that cefazolin may be useful prophylactically and therapeutically in ophthalmology.

TABLE 2

MINIMAL INHIBITORY CONCENTRATION (μg/ml) REQUIRED TO INHIBIT 90% OF ISOLATES FROM VARIOUS STUDIES

Pathogen	Sabath and associates[10]	Bergeron and associates[11]	Kaye and associates[12]
S. epidermidis	0.2		
S. aureus (Penetration sensitive)		0.2	
S. aureus (Penetration resistant)		0.2	
St. pyogenes	0.2	0.1	0.2
St. pneumoniae	0.1	0.1	0.2
E. coli	1.4	6.2	6.3
Enterococcus	25	50	
H. influenzae		6.2	
Klebsiella	6.3	6.2	8.0
Proteus mirabilis	6.3	12.5	12.5
Proteus species (Indole-positive)	200		50
Pseudomonas	400		50

Cefazolin is a broad spectrum antibiotic that appears to penetrate aqueous humor in bactericidal concentrations after subconjunctival injection and may serve as a useful alternative in patients sensitive to other antibiotics.

SUMMARY

We determined the clinical potential of cefazolin by assaying aqueous samples for levels of aqueous penetration of cefazolin in humans and rabbits after subconjunctival injection. Cefazolin is a broad spectrum antibiotic that appears to penetrate aqueous humor in bactericidal concentrations after subconjunctival injection and may serve as a useful alternative in patients sensitive to other antibiotics.

ACKNOWLEDGMENTS

Iva Stinson, B.S., did the bioassay of human aqueous samples; H. R. Black, M.D., and John W. Lamb, M.S., did the bioassay of rabbit aqueous samples.

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PRIMARY CHOROIDAL AND CUTANEOUS MELANOMAS OCCURRING IN A PATIENT WITH THE B-K MOLE SYNDROME PHENOTYPE

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The occurrence of primary malignant melanomas of the choroid and skin in the same patient is a rare phenomenon. We know of only one well documented case[1] and one possible case.[2] We report herein the occurrence of a primary choroidal melanoma and a primary cutaneous melanoma in a patient with the B-K mole syndrome[3] phenotype.

CASE REPORT

A 54-year-old man of Polish extraction was well until January 1976, at which time he developed the gradual onset of painless blurred vision of the left eye. By March 1976, the patient sought ophthalmologic consultation.

The patient had never been exposed to toxic chemicals but had an above average exposure to solar radiation during summer vacations for 25 years. Family history disclosed that his parents, seven siblings, and three offspring had no history of malignancy of any kind. Specifically, there was no family history of skin cancer, melanoma, or ocular malignancy.

When examined on March 22, 1976, his visual acuity was R.E.: 6/6 (20/20) and L.E. 6/9 (20/30). Intraocular pressures by applanation were R.E.: 13 mm Hg and L.E.: 11 mm Hg. The right eye was normal except for numerous superficial iris freckles and a one-disk diameter flat choroidal nevus at the equator superotemporally.

Examination of the left eye showed numerous iris freckles, a dilated episcleral vessel in the ciliary body region inferotemporally, and an 8 × 8-mm pigmented mass easily seen through the dilated pupil on the temporal side. Fluorescein angiography showed early mottled fluorescence and late staining of the mass with slight leakage into the vitreous. B-scan ultrasonography revealed a dome-shaped equatorial mass, measuring 8 × 8 mm with acoustic hollowness. A radioactive phosphorus (^{32}P) uptake test by the transconjunctival technique showed an uptake of 154% (positive for malignancy).[4] Laboratory tests showed normal complete blood cell and platelet counts. Liver function chemistries were normal. Chest x-ray, liver scan, bone scan, and brain scan did not indicate metastatic disease.

Based on the findings of these studies, a clinical diagnosis of primary malignant melanoma of the ciliary body and choroid of the left eye was made. On April 2, 1976, the patient underwent enucleation of the left eye, insertion of a Soll-Dow Corning silicone intraorbital implant, and scleral transplant to the left socket.

Gross examination of the globe showed a normal sized eye with a transillumination shadow measuring 17 × 16 mm inferotemporally. The sectioned globe showed an oval-shaped, irregular pigmented mass located inferotemporally (Fig. 1). The tumor was composed of closely packed, plump, spindle-shaped cells with indistinct cell membranes and oval-shaped nuclei. Melanin granules were present in the cytoplasm of most cells. Some of the nuclei had a central line of basophilic staining and others showed a prominent nucleolus. Occasional cells were more plump and showed abundant eosinophilic cytoplasm and better defined cell margins. Evidence of intrascleral invasion but no extrascleral extension of the tumor was noted. The histologic diagnosis was spindle-B cell type malignant melanoma of the ciliary body and choroid.

On July 12, 1977, the patient was examined at the Melanoma Unit, Fox Chase Cancer Center. Physical examination showed no evidence of recurrent or metastatic choroidal melanoma. Detailed cutaneous examination revealed numerous pigmented lesions scattered about the torso (Fig. 2). These lesions measured 5 to 15 mm in diameter and contained hues of tan, brown, and pink. One pigmented lesion located over the right scapular skin measured 9 × 7 mm, had an irregular border, and contained hues of tan, brown, pink, and white. Excisional biopsy of this suspected pigmented lesion was per-

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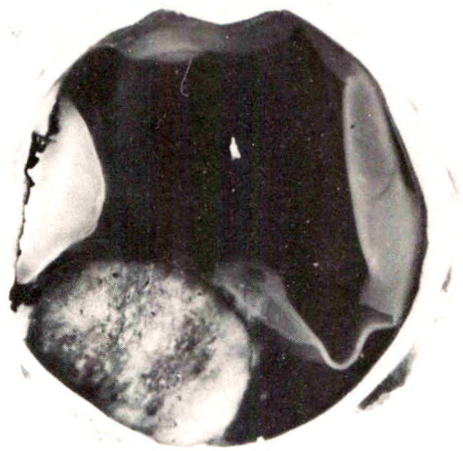

Fig. 1 (Bellet and associates). Sectioned globe revealing an oval-shaped, irregular pigmented mass located in the ciliary body region inferotemporally.

formed on July 21, 1977, along with excisional biopsy of two randomly selected pigmented lesions from the skin of the back.

Histopathologic examination of the pigmented lesion showed a superficial spreading melanoma invasive to Level II, 0.44 mm thick. The two random biopsy specimens were compound nevi with areas of melanocytic dysplasia and were therefore consistent histologically with the appearance of B-K nevi.[3] On Aug. 12, 1977, wide re-excision of the scar over the right scapular skin was performed as definitive therapy for the primary cutaneous melanoma.

The patient has been followed up at three-month intervals from July 1977 to date without physical, laboratory, or roentgenologic evidence of metastatic disease. Additionally, ophthalmologic examination and careful cutaneous examination at three-month intervals failed to show evidence of a new primary cutaneous or primary choroidal melanoma.

Discussion

Primary cutaneous melanoma and primary ocular melanoma are both relatively rare malignancies with incidence rates of 4 out of 100,000 and 1 out of 100,000, respectively.[5] The occurrence of primary cutaneous melanoma and primary choroidal melanoma in a single patient is rare with only two such cases reported.[1,2]

The first reported case[2] was that of a 72-year-old woman who had the simultaneous occurrence of two minimally invasive primary cutaneous melanomas of the periorbital skin of the right eye associated with melanosis of the bulbar and palpebral conjunctiva of the right eye, and a small (2 mm diameter, 0.3 mm elevated) melanocytic tumor of the choroid in the right eye. Although the choroidal lesion was reported as a malignant melanoma, a review of the published photomicrographs suggests that it would be classified as a nevus according to currently accepted histologic criteria.[6] The second case[1] was that of a 64-year-old man who developed a diffuse primary choroidal melanoma ten years after excision of a melanoma of the lip. Our case differs from the previous cases in two respects: (1) the two malignancies involved different regions of the body; and (2) our patient manifested the B-K mole syndrome[3] phenotype.

Fig. 2 (Bellet and associates). B-K nevi and a primary cutaneous melanoma (circled).

In the present case, the presence of

junctional activity in the overlying epithelium in relation to the primary cutaneous melanoma,[7] the histology of the primary choroidal melanoma, and the negligible propensity for minimally invasive primary cutaneous melanomas to metastasize[8] effectively rule out primary choroidal melanoma metastatic to skin and primary cutaneous melanoma metastatic to the choroid.

Data in published reports document the occurrence of primary cutaneous melanoma and primary choroidal melanoma in four families.[9–12] However, in none of these families did both types of malignancies occur in any one patient. Our patient has no family history of either cutaneous or ocular melanoma.

The recent identification of the B-K mole syndrome[3] deserves further comment. Hereditary precursor lesions in cutaneous melanoma patients and their first-degree relatives have recently been described. These lesions are located over both sun-exposed and unexposed skin, are large (greater than 5 mm in diameter), contain hues of tan, brown, and pink, have irregular borders, may progress to invasive cutaneous melanoma, and are microscopically differentiable from common acquired nevi. Histologically, B-K nevi are compound nevi with distinctive changes in the papillary dermis, that is, atypical melanocytic hyperplasia, fibroplasia, new blood vessel formation, and a mononuclear infiltrate. Our patient does not have a family history of primary cutaneous melanoma and therefore must be considered to manifest only the B-K mole syndrome phenotype (unless or until a sibling or child develops a primary cutaneous melanoma).

There are presently no data available as to the incidence of primary choroidal melanoma in patients with the B-K mole syndrome or the B-K mole syndrome phenotype. It is therefore recommended that all patients who have the B-K mole syndrome (phenotype) undergo complete ophthalmologic examination to rule out a primary choroidal melanoma; possibly intraocular melanoma is an associated clinical feature of the B-K mole syndrome. Furthermore, all patients with a diagnosis of ocular melanoma should have careful cutaneous examination to define the incidence of the B-K mole syndrome (phenotype) in this class of patients.

Summary

A patient with malignant melanoma of the choroid and ciliary body had a primary cutaneous melanoma and the B-K mole syndrome phenotype. Because of this newly described association, all patients with the B-K mole syndrome (phenotype) should have a complete ocular examination to discover if there is any evidence of ocular melanoma. Likewise, all patients with ocular melanoma should have a thorough dermatologic examination to determine evidence of cutaneous melanoma and the B-K mole syndrome (phenotype).

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OPHTHALMIC MINIATURE

Of the same kidney are those who court immortal fame by writing books. They don't seem to me favoured by fortune but rather to be pitied for their continuous self-torture. They add, change, remove, lay aside, take up, rephrase, show to their friends, keep for nine years and are never satisfied. And their future reward, a word of praise from a handful of people they win at such a cost, so many late nights, such loss of sleep, sweetest of all things, and so much sweat and anguish. Then their health deteriorates, their looks are destroyed, they suffer partial or total blindness, poverty, ill will, denial of pleasure, premature old age and early death and whatever remaining disasters there may be. Yet the wise man believes he is compensated for everything if he wins the approval of one or other purblind scholar.

Erasmus of Rotterdam
Praise of Folly, 1509

RECURRENT ORBITAL MALIGNANT MELANOMA AFTER THE EVISCERATION OF AN UNSUSPECTED CHOROIDAL MELANOMA

ROBERT A. LEVINE, M.D., ALLEN M. PUTTERMAN, M.D., AND MICHAEL S. KOREY, M.D.

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The extension of a choroidal melanoma into the orbit is usually associated with a rapidly fatal outcome. We describe a man, currently well, who underwent an exenteration for an orbital melanoma 15 years after an evisceration for an unsuspected melanoma of the choroid.

CASE REPORT

In 1964, a 47-year-old man complained of pain of three days' duration in his blind left eye. Examination of this eye showed a nonreactive pupil, posterior synechiae, cataract, and intraocular pressure of 81 mm Hg. The left fundus could not be visualized. The right eye was normal. The ocular history and system review were unremarkable. Because of pain and the failure of the glaucoma to respond to medical therapy, the patient was hospitalized and the eye was eviscerated. The pathologist reported that the eviscerated specimen consisted of "inflammation and hemorrhage."

The patient wore a prosthetic ocular shell without difficulty until 1976, at which time he noted swelling of his left eyelids, enlargement of the left orbital tissues, and frequent, spontaneous extrusion of the ocular prosthesis. In February 1978, the swollen and erythematous left eyelids were displaced anteriorly by a black, firm, and immovable orbital mass (Figs. 1 and 2).

Radiographically, the left orbit appeared slightly deformed and expanded in its transverse diameter (Fig. 3). The enlargement of the orbital cavity in the absence of invasion of the orbital bones suggested the presence of a slow-growing neoplasm. By computed axial tomography, the left orbital tumor showed definite enhancement with contrast media (Fig. 4). No intracranial extension of the tumor was noted.

Fig. 1 (Levine, Putterman, and Korey). Patient's swollen left eyelids displaced anteriorly by orbital mass.

A-scan ultrasonography showed a left orbital tumor of extremely low acoustic reflectivity with ill-defined borders (Fig. 5). These acoustic findings were most consistent with the lymphoma-sarcoma group of orbital tumors.

In February 1978, the left orbit was explored surgically. The black-brown orbital tumor was removed at a biopsy and frozen sections showed the presence of a malignant melanoma. During exenteration of the left orbit, the floor, medial wall, and roof of the orbit were found to be paper thin. In dissecting periosteum, two small penetrating areas were created in the floor and medial walls. Upon severing the apex of the exenterated specimen, we found that

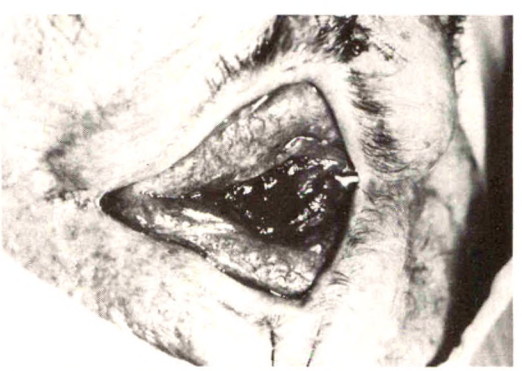

Fig. 2 (Levine, Putterman, and Korey). Pigmented orbital tumor, exposed at time of surgery.

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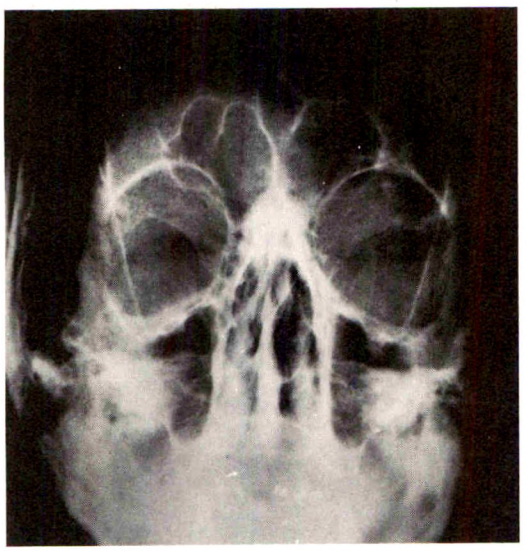

Fig. 3 (Levine, Putterman, and Korey). Transverse expansion of left orbit without bony invasion in conventional orbital x-ray film.

Fig. 4 (Levine, Putterman, and Korey). Computed axial tomogram showing tumor involving and expanding entire left orbit.

tumor tissue had been transsected. The remainder of the tumor in the apex of the orbit was removed piece by piece until all visible residual tumor had been eliminated from the orbit.

Postoperatively, the left orbit healed in a normal fashion (Fig. 6). An examination by the oncology service, including liver-spleen/gallium and bone scans, showed no evidence of metastatic disease. Because of the possibility of residual tumor in the orbit, the left orbit was irradiated; 2,000 neutron rads were delivered in eight divided treatments. The patient also received bacillus Calmette-Guerin immunotherapy. When last seen, 14 months after the exenteration, the patient had no evidence of local recurrence or of metastatic disease.

Sections obtained from the eviscerated specimen of 1964 were examined. These sections showed the presence of a spindle-cell melanoma (Fig. 7), presumably of choroidal origin. The orbital recurrence was also of the spindle-cell variety (Fig. 8).

Discussion

The presence of an intraocular melanoma should be suspected in any white

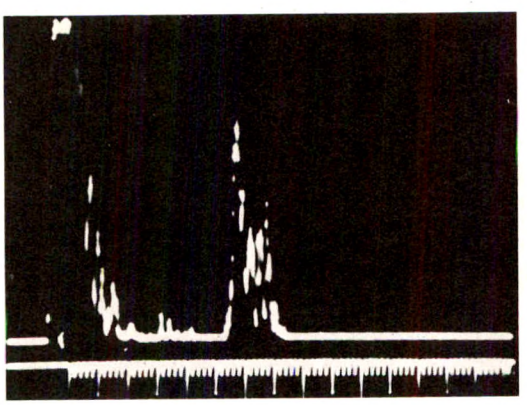

Fig. 5 (Levine, Putterman, and Korey). A-Scan ultrasonography, showing low acoustic reflectivity, compatible with lymphoma-sarcoma group of tumors.

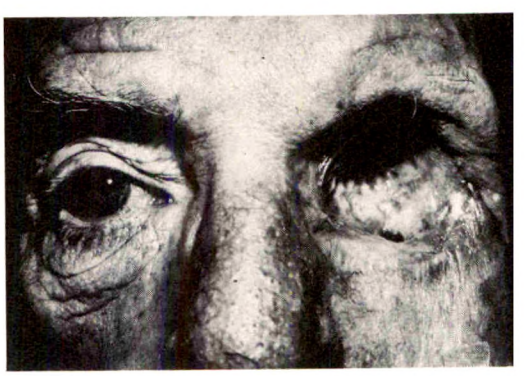

Fig. 6 (Levine, Putterman, and Korey). Patien seven months after left orbital exenteration an radiation treatment.

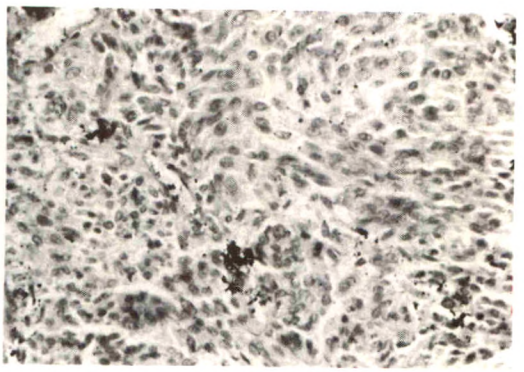

Fig. 7 (Levine, Putterman, and Korey). Review of 1964 evisceration specimen revealed presence of a spindle-cell melanoma, presumably originating within the choroid. Elongated cells with fusiform nuclei are present.

person over age 40 years whose visual loss is associated with unilateral glaucoma and cloudy media.[1,2] Four percent of blind eyes with opaque media contain unsuspected choroidal melanomas.[1] Intractable glaucoma invariably prompts the enucleation of these eyes. Microscopic examination of enucleated specimens has shown that as high as 10% of choroidal melanomas are clinically unsuspected.[3]

In our case, the classic findings that should have aroused the suspicion concerning intraocular melanoma were either discounted or ignored. Additionally, making recurrence or metastasis more likely, an evisceration was done. An early death for this patient should have been anticipated for at least two reasons. First, if the operative manipulation of a melanoma-containing eye fosters early dissemination, certainly evisceration of such an eye would further enhance the likelihood of metastasis.[4–6] Instances of death from metastatic melanoma after the evisceration of an unsuspected intraocular melanoma have occurred.[7,8] Second, the presence of orbital recurrence or extrascleral extension is associated with an extremely high mortality. In the Armed Force Institute of Pathology series,[9] the five-year mortality in their cases with extraocular extension was nearly 70%, emphasizing the rapidly lethal clinical course that characterizes recurrent orbital melanoma.

What then accounts for our patient's survival 15 years after the evisceration of an unsuspected melanoma and development of a bulky orbital recurrence that necessitated orbital exenteration? Reported instances of recurrent orbital melanoma occuring ten,[10] 13,[11] 24,[12] and 28[13] years after enucleation indicate that the presence of an orbital melanoma does not invariably cause a rapidly fatal outcome. Immunologic factors, such as the presence of tumor-associated antibodies, may prevent the spread and growth of metastasis. A more tangible explanation, in our case, is the absence of epithelioid cells within the tumor. A favorable biologic behavior of spindle-cell melanoma has been emphasized by Gass.[14] Our case also supports Gass's contention that spindle cells and epithelioid cells are distinct clones of cells, and that spindle cells seldom dedifferentiate into epithelioid cells.

One might avoid evisceration of an eye containing an unsuspected melanoma. We believe that the evisceration procedure probably did permit the develop-

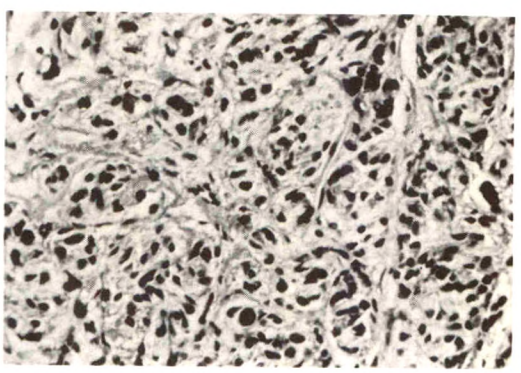

Fig. 8 (Levine, Putterman, and Korey). Exenteration specimen shows densely pigmented melanoma cells of the spindle-cell variety.

ment of an orbital recurrence. Yet, despite the surgical manipulation of the tumor and the orbital recurrence, the patient is still alive, largely because of the apparent cytologic benignity of this melanoma.

Summary

Fifteen years ago a 47-year-old man underwent an evisceration for an unsuspected choroidal melanoma. A bulky recurrence required exenteration. The patient is currently alive and has no evidence of metastatic disease.

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SCANNING ELECTRON MICROSCOPY OF POSTERIOR POLYMORPHOUS CORNEAL DYSTROPHY

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Among the corneal dystrophies affecting the posterior corneal layers, posterior polymorphous dystrophy is of particular interest because of the genetic implications, the appearance in early age, and the apparent variations in the histologic appearance. This disease is characterized by diffuse polymorphic opacities in Descemet's membrane, as noted by Koeppe[1] in 1920, and may eventually progress to corneal edema. A true correlation between the biomicroscopic and the histologic findings has not been available; thus, many authors have described warts,[2–4] cysts or vesicles,[5–8] or pits[5,8,9] in Descemet's membrane. There have been a few electron microscopic studies[8–14] with conflicting observations.

We report the scanning electron microscopic observations in one cornea obtained at the time of penetrating keratoplasty and correlate histologic findings with clinical observations and specular microscopic photography. Our studies confirm those of Grayson[14] in which he showed that some of the most prominent changes were areas of endothelial degeneration and regeneration, as well as abnormality of Descemet's membrane.

CASE REPORT

An 8 1/2-year-old girl was referred for examination of a corneal endothelial dystrophy with bilaterally decreased visual acuity. Her family history was unremarkable except for corneal findings in her mother. Her general health was good.

Results of external eye examination were normal. Her best corrected visual acuity was 6/30 (20/100) in both eyes. Contact lenses did not improve her vision further. Slit-lamp examination of the corneas revealed discrete central stromal haze caused by edema (Fig. 1). The epithelium of both corneas was normal. The endothelium showed diffuse blisterlike

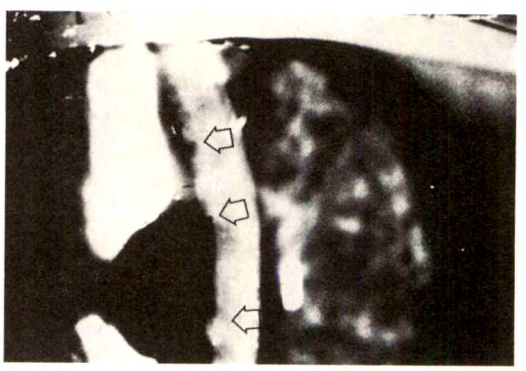

Fig. 1 (Polack and associates). Slit-lamp photograph revealing discrete stromal haze in the central cornea and several defects or pits in Descemet's membrane (arrows).

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changes with a few prominent pitlike formations that were more pronounced in the left eye. Some of the endothelium in the paracentral area of the right eye could be photographed with the specular microscope.

Examination of family members included the patient's mother and maternal grandmother. Her 28-year-old mother had a few blisterlike lesions or pits in the temporal paracentral endothelial portion of both eyes, which were more prominent on the left eye (Fig. 2). Vision was normal in both eyes. The grandmother had normal corneas. No other family members were available for examination, but there was no familial history of eye disease or decreased vision. Because of failure to improve the patient's visual acuity with refraction on several occasions, a 7-mm penetrating keratoplasty was eventually performed in the left eye.

Material and Methods

Specular microscopy—Photographs were taken with a specular microscope[15] using Kodak Tri-X film. Pictures were enlarged and prints were copied to increase contrast.

Corneal specimen—The corneal specimen removed at the time of keratoplasty was immediately fixed in cold 4% buffered glutaraldehyde. The specimen was cut into three portions 16 hours later. The largest portion was used for scanning electron microscopy, and the other two portions were processed for light and transmission electron microscopy.

Light microscopy—The specimen was dehydrated in graded alcohols and embedded in paraffin. Five-micron sections were deparaffinized and stained with hematoxylin and eosin and PAS.

Scanning electron microscopy—After fixation in glutaraldehyde, the tissue was fixed for one hour in 1% osmium tetroxide, then rinsed in phosphate buffer and dehydrated in graded alcohols. The specimen was then dried in a critical point apparatus, and subsequently mounted on an aluminum stub and coated with gold palladium. The specimen was examined with a scanning electron microscope at 20 kV, and photographs were recorded on Polaroid P/N film.

Transmission electron microscopy—After fixation in glutaraldehyde, the specimen was postfixed in 1% osmium tetroxide for 90 minutes, then dehydrated in graded alcohols, and embedded in Epon. Thin sections were examined with an electron microscope.

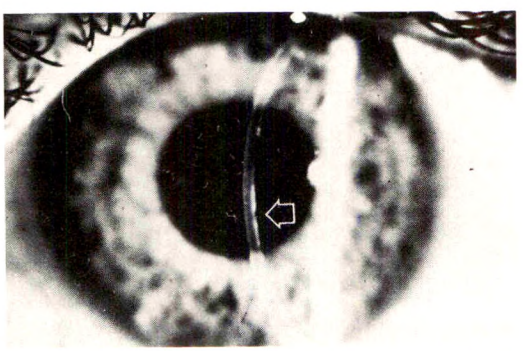

Fig. 2 (Polack and associates). Photograph of the left eye of the patient's mother showing several pits in the posterior corneal surface centrally (arrow).

Results

Specular microscopy—Specular microphotographs were possible in the paracentral area where the edema was minimal. Endothelial cells of normal configuration were evident (Fig. 3, left), but of varied size. Cell junctions were well defined, but there were some areas of darkness between cells or replacing them (arrows). In some areas the dark spots appeared more circumscribed, and they may have comprised several cells, but the arrangement of cells adjacent to these blank areas was not too different from the normal arrangement of cells (Fig. 3, right). Cells of large size were seen in different areas.

Light microscopy—Cross-sections of the corneal button showed a mild degree of edema in the basal epithelial layer. The stroma showed no evidence of inflammation. The posterior corneal layers were outstanding for the presence of depressions or pits. Periodic acid-Schiff-stained sections showed that these depressions were lined with a thinned Descemet's membrane and covered by large or thin

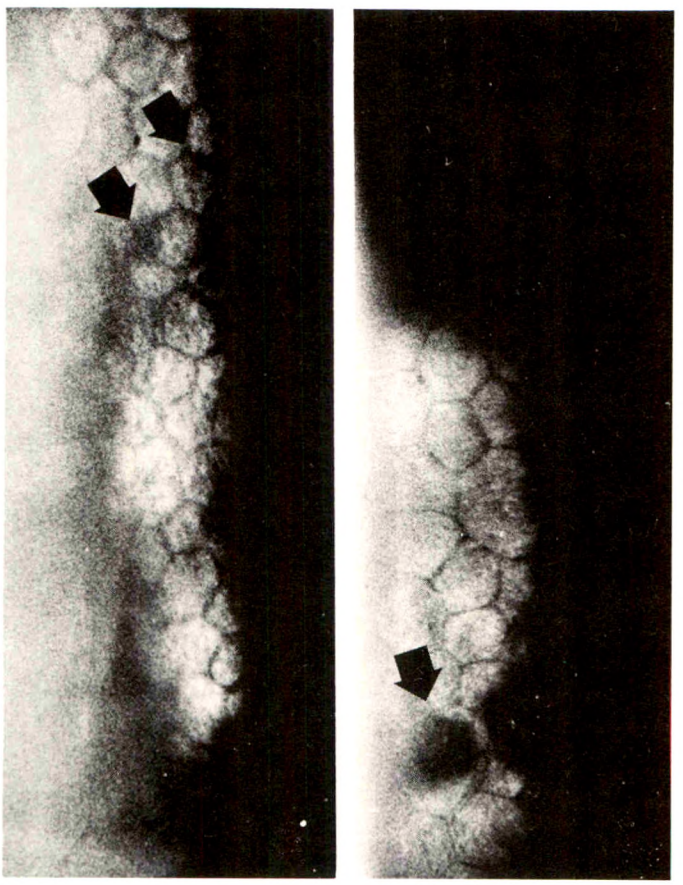

Fig. 3 (Polack and associates). Left, Specular microphotograph of the midperipheral portion of the patient's cornea showing cells of normal configuration, but of varied size. Cell junctions are well defined but there are several areas of darkness within and between cells (arrows). Right, At higher magnification, this photograph shows a well defined dark area of about 10 μ in diameter. This may correspond to a cystic formation comprising one or two cells (arrow).

endothelial cells (Fig. 4). Some of these pits comprised more than two corneal lamellae, and at times, there was a reduplication of Descemet's membrane forming a thickening at the bottom of the pit or at the edges. In other areas, there were bridges and pockets or invaginations of Descemet's membrane and large elongated cells forming more than one layer.

Scanning electron microscopy—Low-power scanning electron microphotographs showed multiple endothelial defects that varied in size from 10 to 15 μ in diameter or larger. Some were rounded and comprised a few cells, and others appeared to coalesce and form large defects. The cells surrounding these defects were attenuated, in various stages of disintegration and residues of cell membranes were seen on top of Descemet's membrane. Elongated cells of fibroblastic appearance were evident with cytoplasmic projections into the bare Descemet's area. These lesions were often surrounded by large endothelial cells, some of them with pits or holes in their cytoplasm or between the cells. Large endothelial defects may explain the dark areas with fuzzy borders seen in specular microphotographs. Figure 5 shows one of the several pits found in the corneal tissue. This defect was about 15 μ in diameter; it was lined by endothelial cells that seemed to arrange in a circular fashion around its sharply delineated and raised borders.

Figure 6 shows a variety of endothelial cell alterations found in the specimens. It

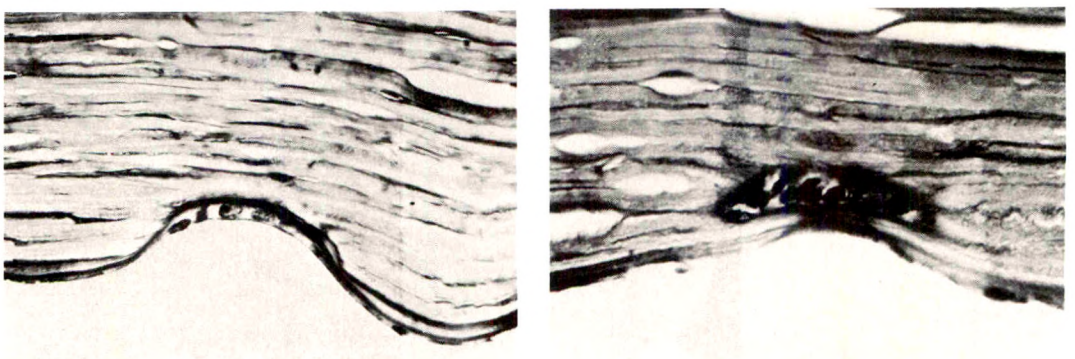

Fig. 4 (Polack and associates). Left, Cross-section of the corneal button showing a depression or pit in the posterior corneal surface. The pit formation is lined by a thin or reduplicated Descemet's membrane and by one or two layers of endothelial cells. The parallelism of the corneal lamellae is interrupted by the formation of this pit (PAS stain, × 200). Right, Cross-section of the cornea in an area where a pit has been partially covered by Descemet's membrane and fibrous tissue. It appears as an invagination of Descemet's membrane; however, this formation is not covered with Descemet's membrane material but with a multiple layer of endothelial-like cells (PAS stain, × 200).

includes areas of anisocytosis, prominent microvilli, abnormal or disintegrating cells, fibroblastlike cells, bare Descemet's membrane and formation of large pit with raised borders. Transmission electron microphotographs showed layering of endothelial cells in some areas, but this was not so obvious in scanning electron microphotographs.

Transmission electron microscopy—Low-power transmission electron microscopy showed the two components of Descemet's membrane; however, they varied in thickness from 9.6 to 12.9 μ. In most sections with abnormal endothelium, it measured less than 10 μ in thickness, and the two layers were often separated by numerous clumps of long-spacing colla-

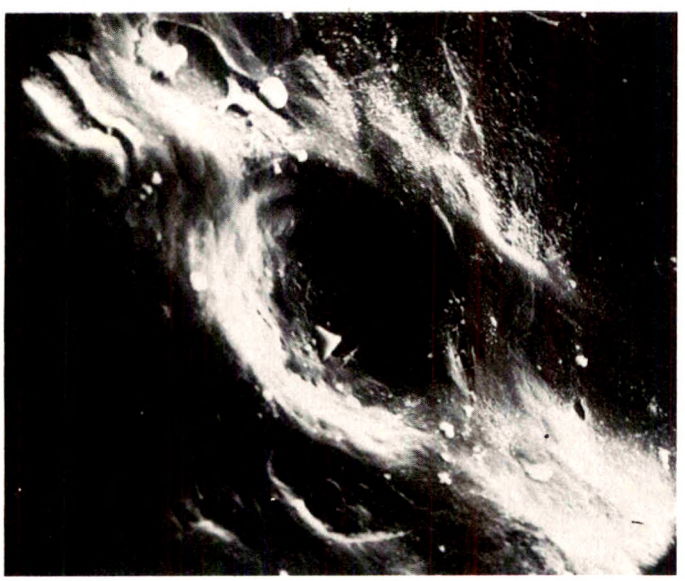

Fig. 5 (Polack and associates). Microphotograph of one of the several pits found in the posterior corneal surface. This defect is about 15 μ in diameter and is lined by endothelial cells that seem to arrange in a circular fashion around its sharply delineated and raised borders (scanning electron micrograph, ×1,000).

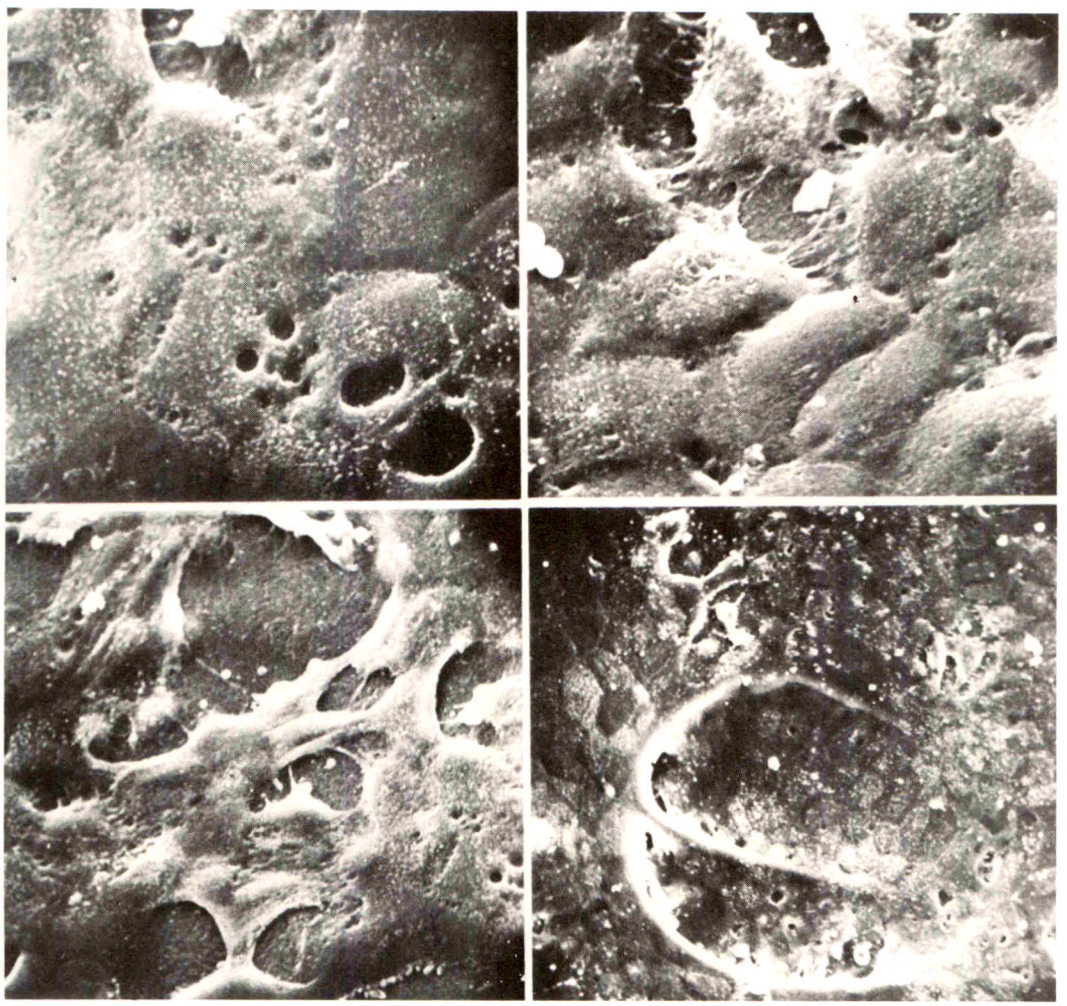

Fig. 6 (Polack and associates). These microphotographs show a variety of lesions found in polymorphous dystrophy. The alterations range from (top left) early degenerative endothelial cell changes and vacuolation (scanning electron micrograph, × 2,000); (top right) separation of cell junctions and baring of Descemet's membrane (scanning electron micrograph, ×1,000) to (bottom left) more advanced degenerative cell changes and evidence of regeneration with appearance of fibroblastic cells (scanning electron micrograph, ×1,000). Bottom right, A depression or umbilicated defect on the posterior corneal surface. This defect is lined with endothelial-like cells and delineated by a ridge of fibrous tissue. Cells tend to insinuate or invaginate under this fibrous ridge (scanning electron micrograph, ×500).

gen (110 nm). Figures 7 and 8 show a Descemet's membrane of irregular thickness with multiple areas of light density in the posterior portion. This portion shows many fine (50 nm) and coarse collagen fibrils, deposited in bundles underneath a single or multiple layer of endothelial cells. The anterior portion was of normal appearance, but thin. Cells that formed only one layer measured about 4 μ in thickness; they had elongated or fusiform shape with numerous microvilli, free ribosomes, and numerous tonofilaments. These predominated in the deeper (posterior) cell layers, whereas prominent organelles, endoplasmic reticulum, mitochondria, and ribosomes predominated in the more anterior layers. A prom-

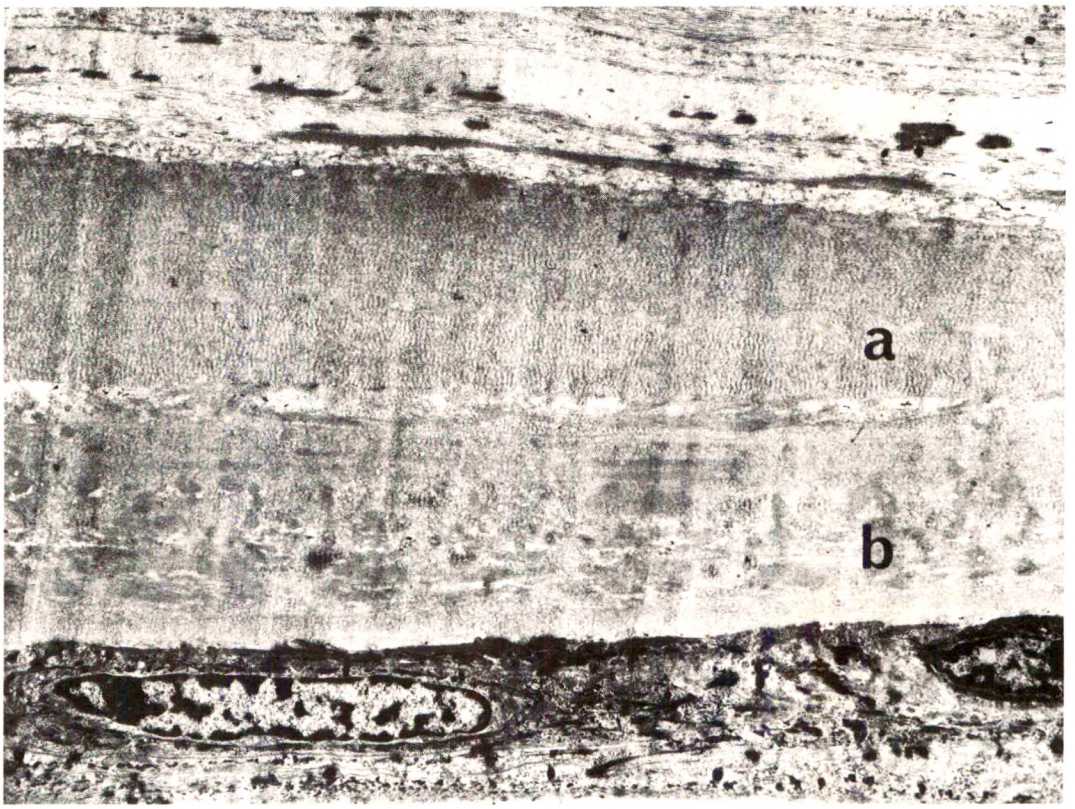

Fig. 7 (Polack and associates). In most areas examined, the thickness of Descemet's membrane varies from 9.6 to 12.9 μ. The two layers of this membrane are clearly visible and are separated by large clefts and deposition of collagen material. Although the anterior portion of Descemet's membrane (a) appears normal except for variations in thickness, the posterior layer (b) is irregular in texture and shows a profuse number of collagen fibrils, deposition of banded collagen material, and clumps of short- (50 nm) and long-spacing (100 mm) collagen. The membrane is covered by two layers of endothelial-like cells, multiple interdigitations, and desmosomal attachments (transmission electron microscopy, ×10,260).

inent finding in these multilayered endothelia was the presence of desmosomal attachments between cells in all layers (Fig. 8). Cell nuclei were elongated with marginal chromatin. Occasionally, macrophages or lymphocytes were found within the endothelial cells.

Discussion

The genetic transmission of posterior polymorphous dystrophy was first shown in 1939 by Theodore,[16] who described the typical blisterlike or pit lesions in a young girl. The transmission is now known to occur as an autosomal dominant trait with high penetrance.[17,18] The pits or blisters may be distributed diffusely or may be mostly central.[19] In recent years, posterior polymorphous dystrophy has been studied ultramicroscopically,[8–14] but those findings have not definitely solved the question about the nature of the anomalies in Descemet's membrane and its endothelium. These electron microscopic studies show widespread alterations in Descemet's membrane that include thinning or reduplication as well as anomalies in the endothelial layer that vary from abnormal endothelial cells to fibroblastic or epithelial-like cells, similar to the ones

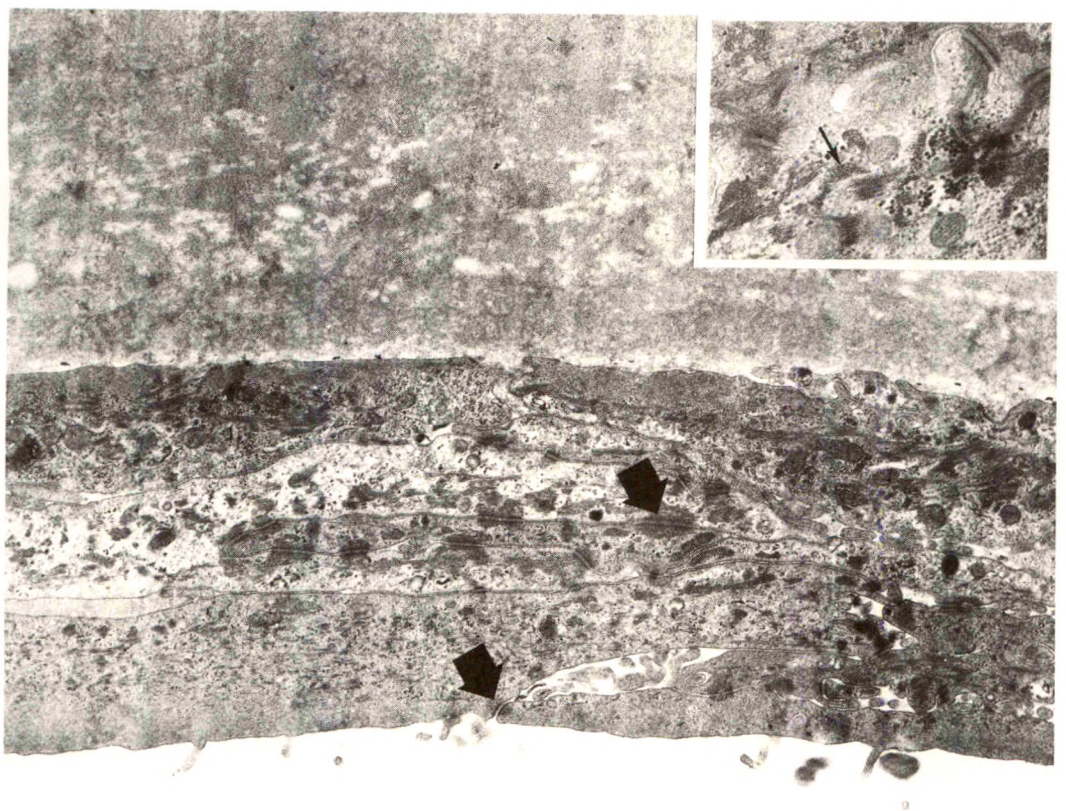

Fig. 8 (Polack and associates). Electron microphotograph of a multiple layer of endothelial-like cells covering Descemet's membrane. The cells are flattened, have numerous interdigitations and the cell walls show multiple desmosomes with tonofilament attachments (arrows). Organelles, tonofilaments, and free ribosomes were profuse in all of these cells; however, the most posterior cells had fewer organelles. Cells facing the anterior chamber show microvilli and desmosomes closing the cell junctions (transmission electron micrograph, ×21,600). Inset shows a profuse number of tonofilaments (arrow), the desomosomal junctions and free ribosome granules (transmission electron micrograph, ×40,320).

found in this case. The association of this type of hereditary corneal disease with other congenital anomalies, particularly with the dysgenesis of the iris and anterior chamber, was described by Grayson[14] in 1974. Iris adhesions to the cornea were reported by others [18,20] as well as myopia, glaucoma,[7–20] and keratoconus.[21] Grayson[14] reported for the first time the ultrastructural surface changes, by scanning electron microscopy, in the endothelial layer of corneas affected with this disease. As in the case reported here, he found that endothelial cells had a large number of microvilli and prominent vacuoles (Swiss cheese appearance) scattered through their cytoplasmic surface. These vacuoles or craterlike holes in the cytoplasm of endothelial cells are not artifactual; we found similar changes in clusters rather than diffusely throughout the specimen as would have occurred if such alterations were the result of poor fixation. The cells that show this vacuolation had abnormal configuration and often were close to areas of cell loss or cell transformation into fibroblastlike elements over a bare Descemet's membrane. Cross-sections of this specimen showed alterations similar to those seen in congenital corneal ede-

ma[13] and formation of pits or PAS-positive hyaline bridges. Because these large pits extended into the corneal stroma, disrupting the continuity of the lamellae, it appeared that some of these defects were congenital. Areas of cell loss, or cell degeneration surrounded by areas of enlarged hypertropic endothelial cells with prominent microvilli suggested that they were involved in a process in which degeneration and attempt at regeneration were both present. This interpretation is supported by transmission electron microphotographs that show prominent endoplasmic reticulum, multilayered cells, and deposition of collagen material that forms a thick posterior Descemet's layer. Similar observations have been made by Johnson and Brown[22] in a case of posterior polymorphous dystrophy and in transmission electron microscopic studies of other corneal diseases where the thickened portions of Descemet's membrane corresponded to new collagen material with deposition of Descemet's membranelike material and clumps of long-spacing collagen.[13,22–29] The nodular formations around the large pits or the PAS-positive bridges and the fibroblastlike cells[24,29] brings up the similarity of these lesions to those of Fuchs' dystrophy, as already reported by others.[8,10,14]

The presence of prominent microvilli, cytoplasmic fibrils, desmosomes, and microorganelles in a case studied by Boruchoff and Kuwabara[10] made them postulate that the endothelial layer was replaced by epithelial cells as a result of embryologic misdifferentiation. Studies by Tripathi, Casey, and Wise,[11] Bron and Tripathi,[12] and Rodrigues and associates[13] also showed similar abnormal cells replacing the corneal endothelium in posterior polymorphous dystrophy, a finding not confirmed by others.[8,14–20,22] However, there is enough ultramicroscopic evidence to show that endothelial cells can, under certain circumstances, transform into fibroblasts or epithelial-like cells.[22,30,24,31] This study supports the above-mentioned observations in that endothelial changes exist in other corneal conditions after inflammation, such as in the stage of retrocorneal membrane formation after graft rejection.[28] This study also confirms the presence of prominent microvilli as described by others.[10,11] By scanning electron microscopy, the cells lining the posterior aspect of the cornea appeared mostly as a monolayer of either endothelial or fibroblastic cells, and they also appeared as a single layer of cells by specular microscopy, even though they actually form a multilayer by light and transmission electron microscopy. We could not confirm the descriptions found in published reports that the main lesions in this disease were vesicles or blisters of different shapes and forms. Possibly, these formations may have existed and were disrupted during the process of corneal excision, but most of the evidence is against this. Although it is possible that some lesions may be cystic at one time, that is, before final rupture of the cell membrane, there are definite anomalies in Descemet's membrane that resemble pits. These or other defects may have formed early in life or as the result of healing and new Descemet's membrane material deposition.[32]

The endothelial changes observed with the specular microscope were, for the most part, identical to those alterations seen with the scanning electron microscope, and such lesions correlate well with the light and transmission electron microphotographs. Unfortunately, the areas of active disease could not be photographed well because of corneal edema. In other cases of posterior polymorphous dystrophy we have seen lesions similar to those described here and more prominent pits in Descemet's membrane.

In corneal diseases, a biomicroscopic appearance may have different causes,

and the same is true for certain histologic appearances. Therefore, possibly several congenital or acquired inflammatory or degenerative conditions may cause alterations in the posterior corneal layers that may appear similar to posterior polymorphous dystrophy under the biomicroscope. This disease, however, has a genetic background; the alterations in Descemet's membrane seem to start early in life[32] and reflect a progressive degenerative process of the corneal endothelium, a possibility previously mentioned by others.[13,22,32]

Summary

An 8½-year-old girl had posterior polymorphous dystrophy that required keratoplasty. Similar lesions were found in the patient's mother, thus establishing the genetic trend of the disease. Scanning electron microscopic studies showed areas of endothelial cell degeneration and multiple depressions or pits. These seemed the most advanced and characteristic lesions of posterior polymorphous dystrophy. Transmission electron microscopic studies in areas adjacent to the pits showed an abnormally developed Descemet's membrane covered by two or more layers of elongated endothelial-like cells. Cells over Descemet's membrane seemed to deposit some Descemet's membrane material and both fine and coarse collagen fibrils. Cells had prominent mitochondria, normal endoplasmic reticulum, and desmosomal attachments. Cytoplasmic fibrils and microvilli were usually found in cells lining the anterior chamber. Specular microscopy and scanning electron microscopy recorded the image of only the innermost cells and these appeared as endothelium.

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Ophthalmic miniature

In his own assessment of himself, written in the third person, Sir Astley Cooper wrote:

Sir Astley Cooper was a good anatomist, but never was a good operator where delicacy was required. He felt too much before he began ever to make a perfect operator.

For the operation of cataract he was quite unfitted by nature.

As an operator for stone, aneurism, hernia and the removal of tumours, prior to his attacks of giddiness, he was excellent, but after that time he was always afraid of being seized with them whilst he operated.

R.C. Brock, *The Life and Work of Astley Cooper*
Edinburgh, E. S. Livingston, 1952

PROGNOSTIC SIGNIFICANCE OF OPTIC DISK CUPPING IN OCULAR HYPERTENSIVE PATIENTS

MICHAEL E. YABLONSKI, M.D., THOM J. ZIMMERMAN, M.D., MICHAEL A. KASS, M.D., AND BERNARD BECKER, M.D.

St. Louis, Missouri

Armaly[1] reported that cup:disk ratio was increased when visual field loss was first detected in patients with glaucoma. He inferred that a large optic disk cup was of prognostic significance in the development of glaucoma and stressed the importance of studying the appearance of the optic disk in ocular hypertensive patients. In retrospective and prospective studies of ocular hypertensive subjects, Wilensky, Podos, and Becker[2] found the cup:disk ratio to be of considerable prognostic value. However, the number of patients in these studies who developed glaucomatous visual field loss was small. Sommer, Pollack, and Maumenee[3] found that 70% of glaucomatous eyes showed vertical contour cup:disk ratios greater than, or equal to, a value of 0.6 at the time glaucomatous visual field loss first became evident. By using multivariate analysis techniques, Hart and associates[4] reported the cup:disk ratio of ocular hypertensive subjects to be among the most important predictors of the development of glaucomatous visual field loss; however, because these statistical methods are of limited applicability for the clinician, the present study was undertaken, using mainly the same subjects as in the study of Hart and associates.[4] In this five-year study of ocular hypertensive individuals, we examined stereoscopic optic disk photographs that were taken before any visual field loss was evident to evaluate further the prognostic significance of the cup:disk ratio.

SUBJECTS AND METHODS

The study included all patients of the Glaucoma Center of Washington University who met the following criteria: (1) older than 45 years of age on June 1, 1972, (2) increased intraocular pressure (IOP) (IOP > 21 mm Hg on three or more occasions in both eyes) and normal visual fields as determined by multiple isopter testing with the Goldmann perimeter, (3) followed up for the succeeding five years, (4) stereoscopic optic disk photographs taken before any abnormality in the visual field was evident, (5) open angles by gonioscopy, and (6) no other ocular disease of consequence.

During the five-year period of the study, the patients had frequent ocular examinations, including applanation tonometry and visual field testing with the Goldmann perimeter. Glaucomatous visual field damage was defined as the reproducible appearance (two consecutive tests) of an arcuate scotoma, paracentral scotoma, or nasal step.

The patients were divided into two groups. Group 1 consisted of 27 patients who developed glaucomatous visual field loss in one or both eyes during the five-year study period. Group 2 consisted of 75 patients who remained free of glaucomatous visual field loss in both eyes for the duration of the study.

From the Glaucoma Center, Department of Ophthalmology, Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by Grant EY 00336 (Dr. Becker) from the National Eye Institute, and by Fellowship Grant PHS Award/Grant No. IF 32EY 0516601 (Dr. Yablonski).

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The stereoscopic photographs were taken by means of a Zeiss fundus camera with the Allen separater. All photographs were obtained before the patient had glaucomatous visual field loss. At the end of the five-year period, the stereoscopic Kodachrome pairs were arranged chronologically for each patient and evaluated in a masked fashion by four independent observers using a stereoscopic viewer. The disks were graded for cup:disk ratio horizontally and vertically by color and by contour, and the numeric grades of the four observers were averaged. When more than one set of photographs existed for a patient, the set closest in date to June 1, 1972, was used as the basis of comparison between the two groups. Subsequent photographs were used only to evaluate progressive cupping. To study progressive cupping, changes in the vertical and horizontal cup:disk ratio by color and contour were noted. Additionally, changes in the relative area of the disk occupied by the cup, ΔA, were calculated from the following equation:

$$\Delta A = r_2^2 - r_1^2$$

where r_1 is the average of the horizontal and vertical cup:disk ratio in the first photograph and r_2 that of the second.

The mean IOP of each eye in the study was determined by averaging all IOP measurements taken after June 1, 1972, before the onset of visual field loss (visual field loss group) or up to the time of the end of the study (no visual field loss group). During this period, the patients were receiving no glaucoma medication.

Results

Twenty-seven patients (Group 1) developed glaucomatous visual field loss in one or both eyes during the five-year study period. For the analysis, only the first eye to develop visual field loss was considered.

Seventy-five patients (Group 2) remained free of glaucomatous visual field loss in both eyes for the duration of the study. For the analysis, the eye with the larger cup:disk ratio was considered. In Group 1 (visual field loss), the initial photographs used were obtained at a mean time of 4.7 years before the onset of glaucomatous visual field loss. In Group 2 (no visual field loss), the initial photographs used were obtained at a mean time of 3.1 years before the end of the study.

No significant difference was found between Groups 1 and 2, regarding age, sex, family history of glaucoma, and incidence of diabetes. Group 1 had a significantly greater frequency of nonwhites than Group 2 (Table 1).

When the cup:disk ratio of the visual

TABLE 1

Demographic characteristics of patients

	Group 1 Visual Field Loss (N = 27)		Group 2 No Visual Field Loss (N = 75)	
	No.	%	No.	%
Mean age (yrs ± S.D.)	60.1 ± 7.2		58.0 ± 8.1	
Men	14	52	40	53
Women	13	48	35	47
Whites	9	33	50	67*
Nonwhites	18	67	25	33*
Diabetes mellitus	3	11	5	7
Family history of glaucoma	11	41	26	35

*Race distribution of Groups 1 and 2 significantly different, ($P < .01$, χ^2 test).

TABLE 2

CUP:DISK RATIO OF EYES IN GROUP 1 (VISUAL FIELD LOSS)* AND IN GROUP 2 (NO VISUAL FIELD LOSS)†

Cup:Disk Ratio Measurement	Group 1 Mean ± S.D.	Group 2 Mean ± S.D.
Horizontal by color	0.53 ± 0.19‡	0.32 ± 0.16
Vertical by color	0.58 ± 0.17‡	0.34 ± 0.17
Horizontal by contour	0.64 ± 0.14‡	0.42 ± 0.16
Vertical by contour	0.69 ± 0.12‡	0.45 ± 0.18

*First eye of each patient to develop visual field loss.
†Eye of each patient with the larger cup:disk ratio.
‡Difference between the means of Group 1 and Group 2 are statistically significant, $P < .01$ (t-test).

field loss group was compared to that of the no visual field loss group, a marked difference was found (Table 2). Whether comparing horizontal or vertical measurements by color or by contour a significant difference was found between the mean values of the two groups.

The grand mean (mean of the individual means) IOP of the first eye that developed glaucomatous visual field loss in each patient of Group 1 was 27.7 ± 5.4 mm Hg (S.D.) compared to 23.6 ± 3.9 mm Hg for the eye with the largest cup:disk ratio of each patient in the no visual field loss group ($P < .01$, t-test).

A scattergraph of the vertical contour cup:disk ratio vs mean IOP for both groups was plotted (Fig. 1). The graph was divided into four quadrants and the points of the two groups showed considerable separation. Only 2% of eyes with a vertical cup:disk ratio of less than 0.6 and a mean IOP less than 28 mm Hg developed glaucomatous visual field loss within five years. At the other extreme, 100% of eyes with a mean IOP of 28 mm Hg or greater and a vertical cup:disk ratio of 0.6 or greater developed visual field loss.

When similar scattergraphs were made from the data of the other three optic disk measurements, the resulting separation was comparable to that obtained using the vertical contour measurement (Fig. 2). The contour data used 0.6 cup:disk ratio as the dividing line, whereas the color data used 0.5, because, as seen in Table 2, the color measurements tended to be 0.1 less than the contour measurements. Summing all four disk measurements produced no

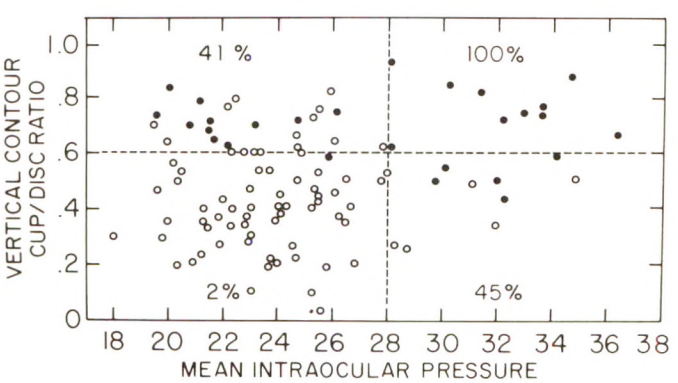

Fig. 1 (Yablonski and associates). Scattergraph of vertical contour cup:disk ratio vs mean IOP. Group 1 (solid circle), First eye of each patient to develop glaucomatous visual field defect. Group 2 (open circle), Eye with largest verticle contour cup:disk ratio in patients who did not develop glaucomatous visual field defect. The percentage of patients in each quadrant who are in the visual field loss group is shown.

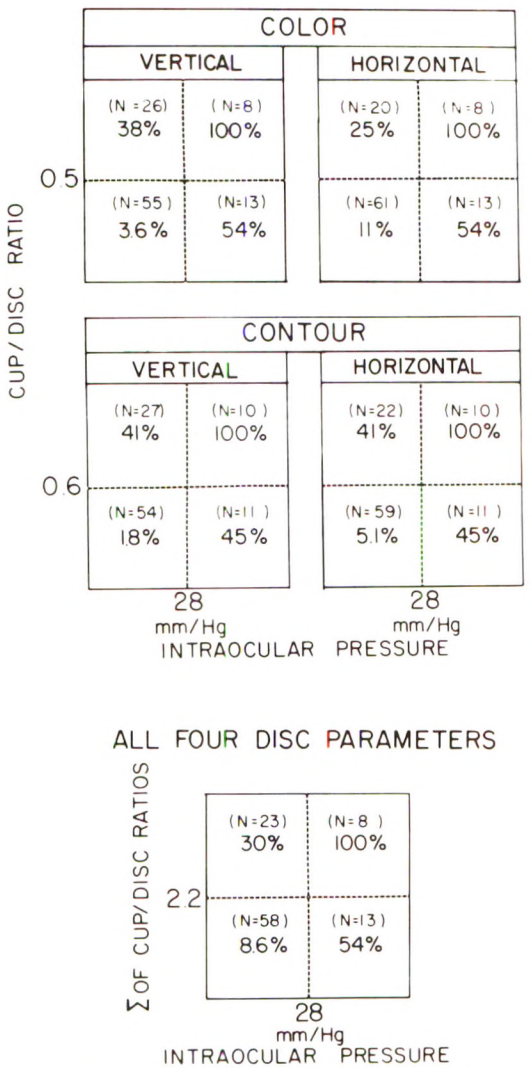

Fig. 2 (Yablonski and associates). The percentage of patients who are in the visual field loss group in each of the four quadrants (as in Figure 1) using each of the four cup:disk ratio factors and their sum. Also shown are the total number (N) of patients in each quadrant.

better separation of the visual field loss and no visual field loss groups than using one measurement alone. The correlation coefficients between the pairs of the four optic disk measures were high in all instances (Table 3).

Eleven fellow eyes in Group 1 had mean IOPs of 22 mm Hg or less up to the time glaucomatous visual field loss was detected in the opposite eye. The mean vertical contour cup:disk ratio in these eyes was 0.62 ± 0.13, significantly different from the mean value of 0.45 ± 0.18 in Group 2 ($P < .01$, t-test).

In both Groups 1 and 2 the frequency of cup:disk ratio asymmetry was more common by contour than by color (Table 4). However, this difference was not statistically significant in any case ($P > .05$, χ^2-test). Group 1 had a higher frequency of asymmetrical cup:disk ratio for all factors than did Group 2. However, the difference was statistically significant only in the cases of the horizontal measurement by color and contour.

Of the 11 patients in Group 1 with contour cup:disk ratio asymmetry of 0.2 or more, ten, (91%) developed visual field loss in the eye with the larger cup. Similarly, of eight patients in Group 1 with color cup:disk ratio asymmetry, six (75%) showed visual field loss first in the eye with the larger cup.

Twenty-four of the 27 patients with visual field loss had disk photographs on two or more occasions before the onset of visual field loss. Forty-eight of the group with no visual field loss had disk photographs on two or more occasions. The mean ± S.D. time between the first and last photographs was 3.1 ± 1.6 years and 3.8 ± 1.7 years in Groups 1 and 2, respectively. The frequency of progressive cupping, based on the cup:disk ratio in one or both eyes before the onset of visual field loss in either eye is shown in Table 5. Although the frequency of progressive cupping was higher in Group 1 than in Group 2 for all four disk measurements, this difference was not statistically significant.

When progressive cupping by area was calculated by the equation, both for color and contour, the incidence of progressive cupping was significantly greater in Group 1 than in Group 2

TABLE 3

CORRELATION COEFFICIENTS BETWEEN THE FOUR CUP:DISK RATIO MEASUREMENTS

	Vertical by Contour	Horizontal by Contour	Horizontal by Color
Horizontal by contour	0.86	—	—
Horizontal by color	0.74	0.75	—
Vertical by color	0.69	0.81	0.91

TABLE 4

NUMBER OF PATIENTS IN WHOM THE CUP:DISK RATIO (ASYMMETRIC CUPPING) OF THE TWO EYES DIFFERED BY 0.2 OR MORE BEFORE GLAUCOMATOUS VISUAL FIELD LOSS IN EITHER EYE

	Group 1 Field Loss (N = 27)		Group 2 No Field Loss (N = 75)	
Cup:Disk Ratio Measurement	No.	%	No.	%
Horizontal by color	6	22*	4	5*
Vertical by color	5	19	6	8
Horizontal by contour	9	33†	9	12†
Vertical by contour	9	33	12	16

*Cup:disk ratio asymmetry more common in Group 1 than Group 2 ($P < .04$, Yates corrected χ^2 test).
†Cup:disk ratio asymmetry more common in Group 1 than Group 2 ($P < .02$, χ^2 test).

TABLE 5

NUMBER OF PATIENTS WHO SHOWED AN INCREASE IN THE CUP:DISK RATIO (PROGRESSIVE CUPPING) EXCEEDING A VALUE OF 0.1 IN ONE OR BOTH EYES BEFORE GLAUCOMATOUS VISUAL FIELD LOSS

	Group 1 Visual Field Loss (N = 24)		Group 2 No Visual Field Loss (N = 48)		Groups 1 and 2 (N = 72)	
Cup:Disk Ratio Measurement*	No.	%	No.	%	No.	%
Color†						
Horizontal	6	25	7	15	13	18§
Vertical	5	21	4	8	9	12§
Contour‡						
Horizontal	12	50	17	35	29	40
Vertical	11	46	16	33	27	38

*Group 1 frequency not significantly different from Group 2 frequency.
†$P > .05$, Yates corrected χ^2 test.
‡χ^2 test.
§Group 1 and Group 2: Contour measurement frequency significantly more than corresponding color measurement frequency ($P < .01$, χ^2 test).

(Table 6). In both groups progressive cupping by contour was more common than by color.

Discussion

Larger optic disk cups are present in eyes that subsequently develop glaucomatous visual field defects. The ability to predict glaucomatous visual field loss improves when cup:disk ratio is combined with the mean IOP. Eyes with a vertical contour cup:disk ratio of less than 0.6 and a mean IOP of less than 28 mm Hg have a low frequency of developing visual field loss within five years in this study (Fig. 1). In marked contrast, eyes with a vertical cup:disk ratio greater than or equal to 0.6 and mean IOP equal to or greater than 28 mm Hg have a high frequency of developing glaucomatous visual field loss in five years.

The separation between the visual field loss and no visual field loss groups is similar using any of the four optic disk factors measured in this study. This similarity reflects the high correlation between the various cup:disk ratio parameters. This correlation also explains the lack of improved separation when the four parameters are combined.

Asymmetric cupping is more common in the visual field loss group. Further indication of the importance of this parameter is the finding that when asymmetrical contour cupping occurs, in 91% of cases, the eye with the larger contour cup develops glaucomatous visual field loss first.

To evaluate progressive cupping, for each individual, disk photographs are arranged chronologically rather than randomly. This is done intentionally to simulate the normal clinical situation; however, as a result, there may be a bias for graders to grade subsequent cups progressively larger. If this bias exists, however, it would overestimate the true incidence of progressive cupping in both Groups 1 and 2. However, the observed incidence of progressive cupping is less than in the study of Somer, Pollack, and Maumenee[5] in which serial disk photographs were randomized and that shows progressive cupping before visual field loss in ten of 12 ocular hypertensive eyes. It must also be considered that in

TABLE 6

Progressive increase in percent of area of disk occupied by cup

	Progressive Increase by Color Percent Area of Disk Mean ± S.D.	Progressive Increase by Contour Percent Area of Disk Mean ± S.D.
	Group 1 (Visual Field Loss)	
First eye to show glaucomatous visual field loss	4.1 ± 5.0%*	8.5 ± 10.9%*†
Other eye	5.1 ± 7.2%*	9.5 ± 11.2%*+
	Group 2 (No Visual Field Loss)	
Eye with larger contour cup	1.3 ± 2.5%	3.7 ± 6.4%†
Eye with smaller contour cup	1.3 ± 2.6%	4.5 ± 7.7%†

*Mean value for Group 1 statistically significantly different from mean value of either eye of Group 2 for same disk parameter ($P < .01$, t-test).

†Mean contour progressive cupping statistically significantly greater than mean color cupping ($P < .01$, paired t-test).

the visual field loss group progressive cupping generally occurs in disks with larger cups than in the no visual field loss group; therefore, an equal change in the linear cup:disk ratio would tend to involve a larger area change of the cup in Group 1 than in Group 2. When this factor is considered, the difference between Groups 1 and 2 becomes significant, indicating the greater loss of tissue in the visual field loss group. Therefore, we concluded that progressive cupping is an important prognostic sign especially when it occurs in an eye with an already large optic disk cup.

The finding that ocular hypertensive individuals with large optic disk cups are more likely to develop glaucomatous visual field loss suggests that these disks have already undergone significant glaucomatous cupping, in the absence of visual field defects. Another possibility is that congenitally larger cups are inherently more susceptible to glaucomatous damage. We could not in this study distinguish between these possibilities with certainty. However, in support of the latter hypothesis is the finding that in 11 fellow eyes in which the mean IOPs are 22 mm Hg or less, in the visual field loss group, the mean vertical contour cup:disk ratio is 0.62, which is significantly larger than the mean value of 0.45 in Group 2 (no visual field loss group). Because these eyes have relatively low IOPs, it seems reasonable to conclude that their disks have not undergone significant glaucomatous cupping.

The reported incidence of the development of glaucomatous visual field loss in patients with increased IOP and normal visual fields varies greatly. Several studies[6-11] showed an incidence of less than 5% in five years. Other studies[12,13] showed an incidence of 16 and 20%. These differences reflect, in part, different diagnostic criteria and methods of subject selection. The high incidence of visual field loss in the present study, 27% in five years, reflects that patients in this study do not represent a random sample of ocular hypertensive individuals. Because ocular hypertensive patients do not all have optic disk photographs, there is likely a bias in the criteria used for inclusion in this study that would result in the inclusion of a disproportionate number of ocular hypertensive subjects with large optic disk cups or high IOPs, or both.

Patients with increased IOP and normal visual fields are not a homogeneous group (Fig. 1). The individuals with cup:disk ratios less than 0.6 and mean IOPs less than 28 mm Hg have a low incidence of glaucomatous visual field loss over a five-year period. Their prognosis does not seem to warrant treatment with antiglaucoma medication. In contrast, those individuals with cup:disk ratios greater than or equal to 0.6 or mean IOPs greater than or equal to 28 mm Hg, or both, have high incidences of development of glaucomatous visual field defects and probably should receive treatment. Prospective studies on more representative ocular hypertensive populations are needed to confirm this recommendation.

The division of ocular hypertensive patients into quadrants is an oversimplification. Patients with obvious glaucomatous disk changes, such as erosion of the rim of the cup,[14] should be considered for treatment regardless of into which quadrant they are classified. The emphasis on contour cup:disk ratio is not meant to minimize the importance of other disk factors, which are somewhat less easily quantifiable than cup:disk ratio. The importance of progressive cupping has been shown. Disk-cup asymmetry is also an important consideration. Kirsch and Anderson[14] reported that glaucomatous cupping tends to occur in the vertical meridian, and they

emphasized the importance of evaluating the rim of the cup, especially at the superior and inferior poles. Schwartz[15] also emphasized the importance of the evaluation of the cup contour. Sommer, Pollack, and Maumenee[5] recently re-emphasized the importance of considering the thickness of the rim of the cup and the importance of the nerve fiber layer, factors we did not evaluate in the present study.

The finding that nonwhites comprise 67% of the glaucomatous visual field loss group compared to 33% in the no visual field loss group suggests that nonwhite ocular hypertensive individuals are more likely to develop glaucoma. Similarly, Hiller and Kahn[16] reported open-angle glaucoma to be more common in blacks than in whites.

Summary

The stereoscopic photographs of 102 patients with increased intraocular pressure (IOP) and normal visual fields were graded for cup:disk ratio. All patients were followed up for a five-year period, during which time 27 patients developed glaucomatous visual field loss and 75 patients did not. The patients who subsequently developed glaucomatous visual field loss had significantly larger cup:disk ratios than did the patients who did not develop glaucomatous visual field loss. Patients with a mean IOP greater than or equal to 28 mm Hg and a vertical contour cup:disk ratio greater than or equal to 0.6 had a 100% incidence of the development of glaucomatous visual field loss as compared to a 2% incidence in those with a mean IOP less than 28 mm Hg and a vertical cup:disk ratio less than 0.6. Disk:cup asymmetry and progressive increase in the area of the disk occupied by the cup was more common in the group that developed glaucomatous visual field loss.

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ORBITAL HEMORRHAGE WITH LOSS OF VISION

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Orbital hemorrhage is a condition not often encountered by the ophthalmologist. Although frequently of insidious onset, it may occasionally occur with dramatic rapidity and serious consequences to the patient's vision . For this reason, it is important to be aware of the entity and its various causes. We encountered a case of orbital hemorrhage that we believe was caused by an intraorbital vascular abnormality, possibly a hemangioma.

CASE REPORT

A 58-year-old woman was referred to us with the symptoms of severe right orbital pain, decreased vision, and proptosis of the right eye, nausea, vomiting, dizziness, and chills of several hours' duration. While playing golf several hours earlier she suddenly had pressure behind the right eye followed by deterioration of vision and bulging of the eye. One month previously she had had an episode of transient right orbital pain while bending over. She was otherwise in good health and denied any illnesses.

She was in acute distress with severe right orbital pain and intermittent retching. Vital signs were normal, and motor and sensory systems were intact. Visual acuity was no light perception in the right eye and 6/4.5 (20/15) in the left eye. Right proptosis was noted with exophthalmos of 7 mm as compared to the left eye by Hertel measurements. The right pupil was dilated at 4 mm and did not react to direct or consensual light stimulation. The left pupil reacted briskly to direct but not consensual stimulation. A complete external ophthalmoplegia of the right eye was noted. Corneal sensation and all branches of the fifth cranial nerve were intact. No bruits were heard in either orbit and no pulsation was evident. A slight blepharoptosis of the right upper eyelid was present. No engorgement of the conjunctival vessels was noted. The applanation pressures were R.E.: 20 mm Hg and L.E.: 15 mm Hg. Retinal examination showed no papilledema or striae.

The patient was admitted to the hospital for further examination. Figure 1 shows her appearance soon after admission. She was examined by a neurosurgeon. A lumbar puncture showed a clear colorless cerebrospinal fluid with normal opening pressure. X-rays of the skull and orbits were normal. Bilateral carotid angiography was interpreted initially as normal. No aneurysm of the internal carotid artery or of the ophthalmic artery was shown (Fig. 2). Computed axial tomography, however, revealed a discrete circumscribed mass greatly attenuated in the right orbit between the optic nerve and the lateral rectus muscle (Fig. 3). The lesion was more attenuated than the surrounding soft tissues. The clinical history and computed tomography scan together indicated that this mass most likely represented hemorrhage compressing the optic nerve.

Because of these findings, a lateral orbitotomy was performed to decompress and explore the right orbit. Retraction of the bone flap and exposure of the lateral rectus muscle and optic nerve resulted in release of serosanguineous fluid. Palpation within the muscle cone into the orbital apex failed to reveal any mass. A biopsy specimen of central conal tissue was reported as "segments of loose fibrous fatty tissue."

The postoperative course was uneventful. The right eye did not recover vision. The visual field was normal in the left eye. Further evaluation of the angiograms by means of subtraction studies revealed enlarged feeding vessels to a region of hyper-

Fig. 1 (Petrelli, Petrelli, and Allen). Right eye, Clinical appearance showing proptosis, blepharoptosis, and dilated pupil. The subconjunctival hemorrhage appeared after hospital admission.

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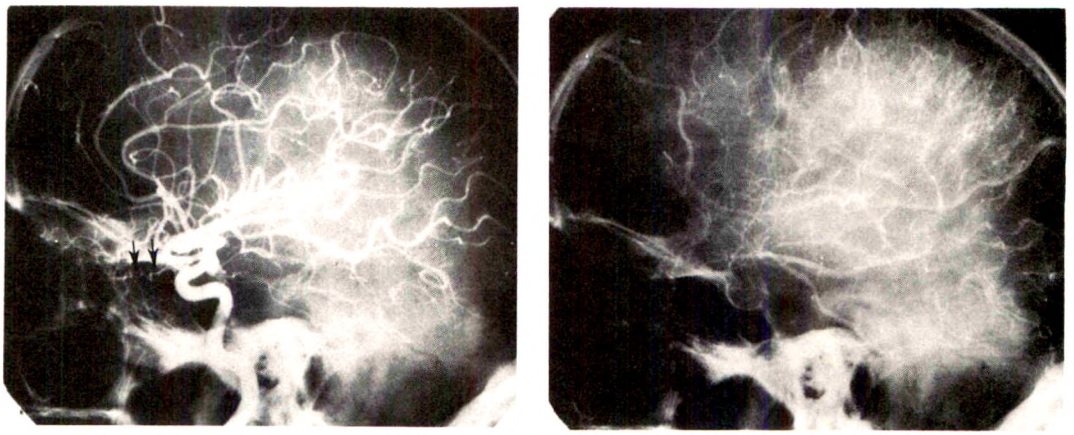

Fig. 2 (Petrelli, Petrelli, and Allen). Right internal carotid angiogram. Left, Arterial phase. The ophthalmic artery (arrows) and its branches appear normal. Right, Venous phase showing no evidence of abnormality.

vascularity with early filling of venous sinusoids, and residual blush in the orbit (Fig. 4). Nine months after surgical exploration a second computed axial tomogram showed a much reduced mass in the right orbit (Fig. 5). The patient continued to be asymptomatic with conservative management.

Discussion

Krohel and Wright[1] recently reported the clinical findings in 17 patients with orbital hemorrhage. Although some patients had a painless, space-occupying lesion developing over a period of months, most had an acute onset of the hemorrhage. The patients ranged in age from 2 to 80 years and there were twice as many females as males. Proptosis ranged from 1.5 to 16 mm, and eyelid ecchymoses were present in eight cases. Pain in 12 cases and vomiting in nine cases was noted. Nine patients had limitation of extraocular movements, four had disk edema, and two had choroidal folds. Associated factors included one case of hypertension, one of anemia, one of Willebrand's disease, and a woman in the second stage of labor. Venograms were abnormal in nine out of ten cases, showing varices in five cases, a mass lesion in three cases, and hypervascularity in one case. Blood cysts were shown pathologically in five cases. The authors stated that the visual prognosis in older patients was poor as irreversible visual loss was too rapid to allow effective treatment, whereas the prognosis in younger patients was much better, especially if immediate surgical drainage was done.

Fig. 3 (Petrelli, Petrelli, and Allen). Computed axial tomograph showing a large mass of high attenuation within the muscle cone of the right orbit. The optic nerve is displaced medially.

Wright[2] had reported earlier that of 627 cases of orbital disease observed between 1968 and 1973, vascular causes of proptosis ranked third (67 cases) after thyroid dysfunction and fractures. Of these 67 cases, congenital primary varix was most common (31 cases). Among those with varices, proptosis was first noted any time

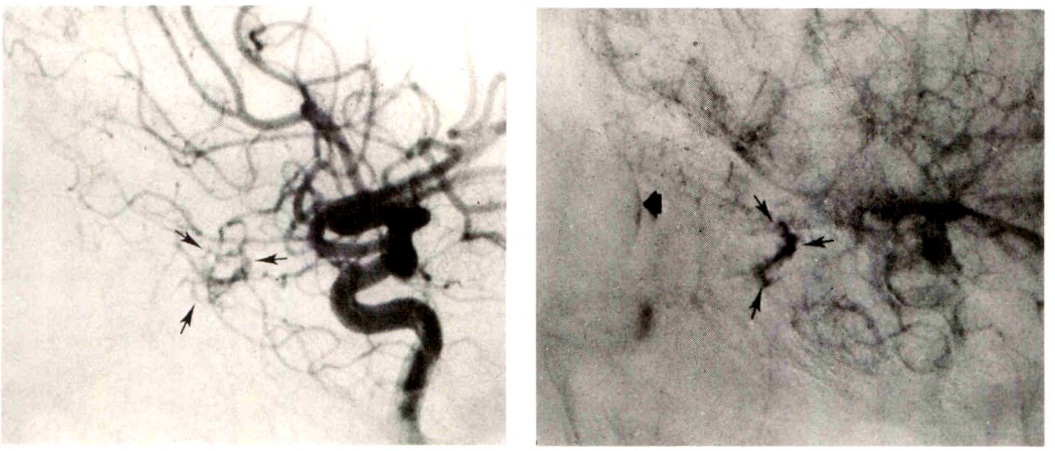

Fig. 4 (Petrelli, Petrelli, and Allen). A subtraction study of the right internal carotid angiogram. Left, Arterial phase showing an area of hypervascularity with enlarged feeding vessels and early venous filling (arrows). Right, Venous phase showing a residual blush of contrast material (thin arrows) which is thought to represent venous sinusoids characteristic of hemangiomas. Note the position of the choroidal crescent (thick arrow).

from birth to early childhood and was often associated with dilated veins in the eyelids, episcleral tissues, or elsewhere in the body. The proptosis increased with crying or coughing and became static in late adolescence. In one case of unsuspected varix, the patient had sudden painful proptosis with vomiting after which orbital hemorrhage was noted. On plain roentgenograms, common findings were orbital enlargement and phleboliths. Orbital venography was most important diagnostically. Carotid arteriography showed displacement of the ophthalmic artery.

Fig. 5 (Petrelli, Petrelli, and Allen). Computed axial tomograph, obtained nine months after surgery, showing a small residual mass in the apex of the right orbit.

Cavernous hemangioma (ten cases) was the next most common vascular cause of proptosis. These patients were older, ranging in age from 35 to 70 years and the proptosis developed more slowly (from two to 25 years). In all patients the pedicle of the hemangioma originated in the superior orbital fissure. Venography and carotid angiography subtraction studies delineated the tumor and helped to differentiate it from orbital varix and lymphangioma, which was sometimes difficult before the advances in contrast radiology.[2] Lloyd[3] believes carotid angiography subtraction studies may be totally diagnostic of hemangioma, showing a fine network of vessels, a feeding arterial supply from a vascular pedicle originating from the superior or inferior orbital fissure, and contrast pooling. Any mass lesion may also produce flattening of the choroidal crescent.

A cavernous hemangioma may hemorrhage, forming a blood cyst that may simulate a superior orbital fissure syn-

drome.[4] Hood[5] described a patient with orbital cavernous hemangioma who was originally thought to have had an orbital hemorrhage. Outside the capsule of the hemangioma were thin-walled cavernous vessels apparently in the process of being incorporated into the lesion, which may explain not only the means by which a hemangioma enlarges, but also how it may hemorrhage.

Orbital lymphangiomas[4] may also cause proptosis, which is usually under 10 mm and slowly progressive. A frequent event is hemorrhage into the lymphangioma ("chocolate cysts") that can appear as a subconjunctival hemorrhage or proptosis. Muscle imbalances are common. Optic atrophy may occur with optic nerve compression. Although often difficult to distinguish from hemangiomas, lymphangiomas are less likely to regress and more likely to infiltrate and hemorrhage as they are not so encapsulated as hemangiomas. A rare variant of the angiomas, which should be mentioned, is the hemangiopericytoma.

Aneurysm is an important cause of proptosis and orbital hemorrhage. Intracavernous aneurysms[6] occur more commonly in women older than age 50 years. They can arise from the cavernous branches of the internal carotid artery or the ophthalmic artery. The first signs and symptoms depend on the size and location of the aneurysm which, as it enlarges, may cause palsies of the third, fifth, and sixth cranial nerves associated with severe orbital pain. The pupil may be mid-dilated or small and immobile depending on the degree of involvement of the parasympathetic and sympathetic fibers.

If the aneurysm ruptures, a carotid-cavernous fistula[6] may develop. Pulsating exophthalmos with orbital bruits and conjunctival venous congestion are the usual signs. Visual loss is a common, devastating consequence and may be immediate or gradual, with retinal ischemia often evident. Ruptured aneurysms, where the ophthalmic artery originates from the internal carotid artery, have resulted in intraorbital bleeding.[4]

Aneurysms of the intraorbital part of the ophthalmic artery occur rarely.[7] The clinical signs may be similar to those of the other aneurysms described. Pain, proptosis, and sudden loss of vision caused by optic nerve compression may follow rupture of such an aneurysm. Any patient in whom the diagnosis of an aneurysm is possible should have cerebral arteriography, which is diagnostic.

Lloyd[13] distinguished primary orbital varices (congenital varix) from secondary orbital varices. The latter type may be an orbital manifestation of a carotid-cavernous fistula or an arteriovenous malformation. Such malformations may be intracranial or intraorbital. The symptoms of the fistula and malformation are similar. In the malformation there is no capillary bed between the artery and vein. It may be congenital, spontaneous, or traumatic. It is rare and less of a threat to vision than the carotid-cavernous fistula.

Trauma should always be considered in the differential diagnosis of orbital hemorrhage, as it can be overlooked and is, indeed, its most common cause.[1] In other patients one may find associated conditions such as leukemia, hemophilia, various clotting disorders, sickle cell disease, and malaria.[4] Finally, there are certain cases of spontaneous orbital hemorrhage in which there are no associated local or systemic diseases.

In our patient, the sudden onset of severe pain, proptosis, external and internal ophthalmoplegia, and rapid loss of vision was compatible with a vascular accident. No bruit or ocular pulsation as in an arteriovenous fistula was noted. No retinal striae or circulatory disturbances as might be expected in an expanding orbital mass were evident. The conjunctival hematoma appeared after hospital admission.

The preliminary carotid angiogram was normal, which ruled out any aneurysm from the cavernous sinus to the orbit. The

computed tomography scan, however, revealed a 12-mm mass in the middle and posterior aspect of the orbit between the lateral rectus muscle and optic nerve that was being displaced medially. Because it was more attenuated than the surrounding soft tissues, the mass was interpreted as hemorrhage. Further evaluation of the angiogram by means of a subtraction study revealed an area of hypervascularity with enlarged feeding vessels and early filling of venous sinusoids with a residual blush. This appearance was most consistent with a hemangioma in this area of the orbit. The preliminary angiogram did not reveal the vascular abnormality, which is often the case with these lesions usually because of the slow circulation within them.[8] Subtraction studies are necessary to elucidate such vascular abnormalities.

At surgery no mass was observed or palpated. Nine months later, a second scan showed a small residual mass in the apex of the orbit. We hypothesize that at the time of surgery the hematoma was removed and the ruptured lesion was too small to identify. The posterior location of the lesion adjacent to the optic foramen resulted in optic nerve compression with loss of vision when the lesion ruptured within the enclosed space. These findings indicated an orbital apex syndrome. Should the patient become symptomatic, a more extensive surgical procedure may be indicated.

Summary

A 58-year-old woman had the sudden onset of unilateral painful proptosis, ophthalmoplegia, vomiting, and loss of vision. Computed axial tomography showed a mass that was greatly attenuated in the orbit. The initial reading of the internal carotid angiogram was normal, but a subtraction study showed a hypervascular lesion within the orbit with features indicating a hemangioma. Orbital decompression failed to restore the vision as intraorbital hemorrhage had irreparably damaged the optic nerve.

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Shelby J. Galloway, M.D., provided the films of the cerebral angiograms, and Anthony Parisi, M.D., referred the patient to us.

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EXERCISE-INDUCED INCREASE OF INTRAOCULAR PRESSURE IN THE PIGMENTARY DISPERSION SYNDROME

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The pigmentary dispersion syndrome is characterized by a loss of pigment from iris pigment epithelium, iris transillumination and a characteristic deposition of pigment on the lens, corneal endothelium, and angle structures. In some cases, there is an association with increased intraocular pressure (IOP) that Sugar and Barbour[1] first described as the distinct entity, pigmentary glaucoma. The role of the dispersed pigment in the cause of the glaucoma is still uncertain.

There is evidence that the pigment may be responsible, in part, for the increased IOP. In vivo infusion of a saline suspension of uveal pigment into the anterior chamber increases IOP in human eyes.[2] Similarly, uveal pigment suspended in saline and placed in the anterior chamber causes a decrease in facility of outflow.[3]

Several reports indicate that pupillary dilation with release of iris pigment is associated with increased IOP.[4,5] This would seem to implicate obstruction to outflow by pigment as a factor in increasing IOP. Although mydriasis induced by phenylephrine does not increase pressure in every case, Epstein, Boger, and Grant[5] believe that

> the rise in IOP that can be induced by phenylephrine supports the concept that pigment particles under certain circumstances temporarily obstruct the aqueous outflow channels.

We describe a patient with pigmentary dispersion syndrome who showed an association between exercise or darkroom provocation and increase of IOP. These findings also implicate pigment obstruction to outflow as a cause of the increased pressure in pigmentary dispersion syndrome.

CASE REPORT

A 32-year-old man had blurred vision and colored halos around lights after vigorous exercise, particularly after playing basketball. He also noted similar symptoms during periods of emotional stress and on several occasions while sitting in a darkened room. A paternal uncle had glaucoma.

Ocular examination revealed visual acuity of 6/6 (20/20) in both eyes with correction ($-3.50 + 1.50 \times 180$ in the right eye; and $-3.50 + 1.50 \times 10$ in the left eye). Extraocular movements and results of external examination were normal. The corneas were normal and did not show Krukenberg's spindles. The anterior chambers were normal and deep (R.E.: 3.8 mm and L.E.: 4.4 mm). The pupils were equal with normal responses to light and near. A ring of small wedge-shaped areas of transillumination in the periphery of the left iris was evident. Gonioscopy showed wide open angles in both eyes with dense bands of trabecular pigmentation, which was greater in the left eye. No contusion deformity or excessive iris processes in the angles were evident. Intraocular pressures were R.E.: 25 mm Hg and L.E.: 39 mm Hg.

The right fundus was normal. The left fundus had a vascular anomaly at the temporal margin of the disk. It consisted of a cluster of grapelike venous structures that appeared to attach to the superotemporal vein. The vein was congested, cyanotic, and did not pulsate with pressure on the globe. There was no cupping of either optic nerve head.

Goldmann visual fields were normal. Fluorescein angiography was normal. Tonography revealed C values of R.E.: 0.19 and L.E.: 0.09. Contact B-scan of the eyes and orbits was normal.

The patient underwent a darkroom provocative test. After a period of sitting in the dark for one hour, the patient's IOP increased from 28 to 37 mm Hg in the right eye and from 37 to 52 mm Hg in the left eye. The angles remained wide open with no iris

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crowding. Moderate dispersion of pigment could be observed within the anterior chambers.

The patient was requested to return for examination after a period of strenuous exercise. He returned after two hours of playing basketball and complained of blurred vision and halos. Examination showed pressures of R.E.: 31 mm Hg and L.E.: 54 mm Hg. A small number of pigment floaters were seen in the right anterior chamber and heavy pigment dispersion was noted in the left anterior chamber. Gonioscopy showed no change in the width of the angles.

Pilocarpine 0.5% was prescribed to be used before exercise. He has not been symptomatic after exercise since using this medication prophylactically. When examined after vigorous exercise preceded by treatment with pilocarpine, the IOPs were 30 mm Hg in both eyes despite the presence of dispersed pigment in the anterior chambers.

Discussion

Our patient showed several clinical features that seem to clarify the cause of pigmentary glaucoma. He became symptomatic after strenuous exercise. We were able to show an increase in IOP after exercise that coincided with release of pigment into the anterior chamber. Pretreatment with pilocarpine suppressed the symptoms and prevented an increase in pressure after exercise, even though it did not prevent an increase in pigment dispersion.

The increase in IOP and increased pigment dispersion associated with exercise implies that released pigment can impede aqueous drainage. The protective effect of prophylactic treatment with pilocarpine suggests that by increasing trabecular outflow, it is possible to negate the effect of pigment on IOP. To the best of our knowledge, this is the first report to show the value of pretreatment with pilocarpine drops in this type of patient. Several studies of trabecular meshwork removed at trabeculectomy in patients with pigmentary glaucoma have shown clogging of trabecular spaces and endothelial cells with uveal pigment, which have provided the pathologic correlation for our clinical findings.[6,7] Patients are seen with marked trabecular pigmentation on gonioscopy, but with normal IOP. This suggests that there are some trabecular meshworks inherently more susceptible to the effect of mechanical insults, such as pigment clogging.

Our patient also reported an association of symptoms with emotional upset or prolonged exposure to darkness. He had a significant increase of IOP after a provocative darkroom test in the presence of wide open angles. Epstein, Boger, and Grant[5] described a patient with symptoms brought on by similar conditions who had increased IOP after working in dim light. Their patient had a negative response on formal darkroom testing.

The increase in IOP associated with emotional stress or dim illumination also suggests mydriasis-induced pigment release as the mechanism. Sugar[8] suggested that pupillary dilation leads to increased IOP by mechanical narrowing of already functionally compromised trabecular spaces by an angle-crowding effect. It seems more reasonable that as the pupil dilates, there is mechanical abrasion of the iris pigment epithelium with release of pigment into the aqueous, which impairs trabecular outflow. Our patient showed no crowding of the angles associated with a darkroom-provoked increase of IOP. Campbell[9] proposed that mechanical abrasion of iris epithelium against anterior zonules resulted in pigment release in the pigmentary dispersion syndrome.

We believe that the clinical findings in this patient are consistent with pigment obstruction of trabecular outflow as a pathogenic factor in the increase of IOP. Our case shows a direct association between release of pigment and increased IOP. Pigment release appears to be associated with situations that result in significant iris movement. Although pigment release can cause increased IOP, it may not be the sole cause of the glaucoma associated with pigmentary dispersion syndrome.

Summary

A 32-year-old man with pigmentary dispersion syndrome had blurred vision and halos after strenuous exercise, associated with a release of pigment into the anterior chamber and increased intraocular pressure (IOP). Additionally, he had typical symptoms after emotional stress or exposure to dim illumination, and had a high IOP without angle closure during a darkroom provocative test. The exercise-induced symptoms and the increase of IOP were prevented by the use of pilocarpine 0.5% drops immediately before exercise.

Acknowledgment

Arthur Wolintz, M.D., referred this patient to us.

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NOTES, CASES AND INSTRUMENTS

ONSET OF THE EXFOLIATION SYNDROME AFTER INTRACAPSULAR LENS EXTRACTION

H. SAUL SUGAR, M.D.
Detroit, Michigan

In 1976, as the result of observations on a unique case[1,2] of the exfoliation syndrome, I suggested that the theory of Bertelsen, Drablos, and Flood,[3] which is that fibrillar material from the lens epithelium passed through the amorphous and fibrillar layers of the capsule and appeared as bush-shaped material on the lens surface, was not correct. I further suggested that the material on the lens surface is deposited there from contact with the diseased iris pigment epithelium and probably also indirectly from the ciliary epithelium, but that the material formed in the lens cannot penetrate the fibrillar layer and the zonular lamella. As evidence for the iris-pigment-epithelial or ciliary-epithelial source of the exfoliative material, I described the case of an 89-year-old woman with bilateral exfoliation syndrome in whom the exfoliative material on the hyaloid increased in both eyes over a period of 15 years after uneventful intracapsular cataract extraction.

Since the publication of this report,[1,2] I have seen two patients who had no evidence of the exfoliation syndrome when the intracapsular lens extractions were done but in whom exactly the same type of material has appeared after the lenses were removed. One was unilateral, the other was bilateral. The material was exactly the same as that seen in the patient described previously with continuing formation of exfoliative material on the anterior surface of the hyaloid.

CASE REPORTS

Case 1—A 69-year-old man was first seen in August 1949. He had posterior subcapsular cataracts that were not ready for extraction until July 1960 (left eye) and July 1961 (right eye). No exfoliative material was observed until February 1970 when early ring-like deposits at the pupil border and anterior hyaloid were noted in the right eye only (Fig. 1). This increased slightly but definitely from 1977 to 1979.

Case 2—An 80-year-old man was first seen in June 1951. He had congenital central posterior polar opacities with rings like those in a tree cross-section (Fig. 2). Visual acuity was correctible to 6/12 (20/40) in each eye. The opacities slowly increased so that in June 1963 the right lens was extracted. An adhesion between the lens and hyaloid was present but the

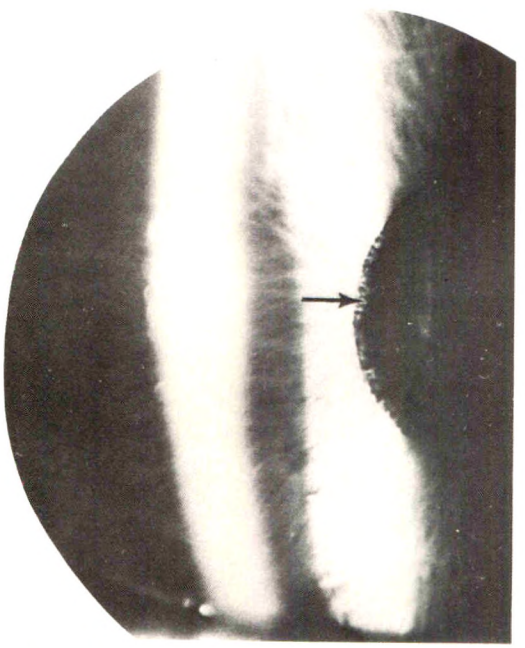

Fig. 1 (Sugar). Case 1. First appearance of exfoliative (arrow) material in right eye nine years after intracapsular cataract extraction.

From Wayne State University School of Medicine, Sinai Hospital of Detroit, and Henry Ford Hospital, Detroit, Michigan.

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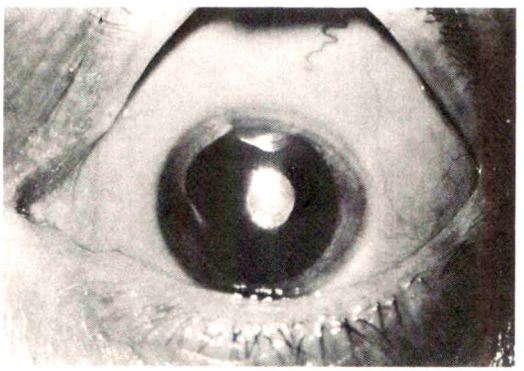

Fig. 2 (Sugar). Case 2. Congential central posterior polar cataract (same in each eye before cataract extraction). Adhesion between lens and hyaloid was present in each eye. No vitreous loss but a central hole in hyaloid in each eye was present.

Fig. 3 (Sugar). Case 2. Right eye, First appearance of exfoliative material 14 years after intracapsular cataract extraction.

extraction was uneventful. Postoperatively, I could see a small central hole in the hyaloid. Six months later the left lens was extracted. The patient had a central lens-hyaloid adhesion. A similar hole in the hyaloid was present postoperatively. Visual acuity was correctible to 6/6 (20/20) in each eye. The pupils and media were clear and only in August 1977 was bilateral exfoliative material noted on the hyaloid at the pupil border in the form of rings of ropy material. When examined again in August 1979 the material had increased in quantity (Fig. 3).

Discussion

Gifford[4] first suggested that the germinal epithelium and the cuticular portion of the lens capsule play no part in the exfoliative (or pseudoexfoliative) syndrome. Radian and Radian[5] in 1975 noted pseudoexfoliative material several years after cataract extraction in three eyes that had shown no evidence of the syndrome before or immediately after surgery. Gillies,[6] however, believed that lens extraction caused the pseudoexfoliative material to diminish and regress. Perhaps if Gillies' cases were observed longer his findings would have been otherwise.

Summary

Two patients who had previously been operated on for cataract and had been carefully observed for evidence of the exfoliation (or pseudoexfoliation) syndrome had continuing formation of exfoliative material on the anterior surface of the hyaloid and the pupil border several years later.

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MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

ASSOCIATION OF UNIVERSITY PROFESSORS OF OPHTHALMOLOGY

The Association of University Professors of Ophthalmology (AUPO) held its 14th annual meeting, under the presidency of Robert D. Reinecke, at Palm Springs, California, Jan. 27-30, 1980. More than 100 chairmen of university units of ophthalmology and program directors of hospitals with residency programs attended. They constituted the majority of the directors of the 150 institutions with ophthalmology residency programs in the United States. The weather, as has become nearly traditional for this meeting, was exceptional for Southern California, with rain and floods, which almost isolated Palm Springs.

The members discussed a variety of topics important to the management of academic units and residency programs. August Colenbrander told of the impressively successful residency ophthalmology matching program. Some 726 individuals participated to obtain 458 first-year residency positions. All but one of the institutions offering residencies participated.

Richard Ruiz chaired a seminar on department management with emphasis on providing efficient, prompt, and competent ophthalmic care. Edward Norton told of departmental fund raising carried out in harmony with university development officers; Herbert Kaufman discussed the research grants program of the National Institutes of Health. The perennial problems of ophthalmology in Veterans Administration hospitals were discussed. Ephraim Friedman, Dean of Albert Einstein College of Medicine, at the annual dinner spoke on the need to bring ophthalmic teaching into the day-by-day activities of medical students as future physicians.

Ronald Geller, Associate Director for Extramural and Collaborative Programs for the National Eye Institute, told of the activities of the Institute. The number of physicians listed as principal investigators of research grants continues to decrease. There is a corresponding decrease in the application of basic science studies to clinical problems. The decrease in patient-oriented research, of course, reflects the congressional mandated decrease in funds to train physicians competent to plan and carry out required clinical research. Bruce Spivey outlined the ambitious plans of the American Academy of Ophthalmology. (All should note that the 1980 meeting of the Academy has been moved to Chicago, Nov.2-7.)

Bradley Straatsma described the American Board of Ophthalmology and the smooth transition of the Secretaryship from Francis Heed Adler to Robert N. Shaffer (the American Board mailing address is unchanged). Alfonse Cinotti described the multiple programs of the American Association of Ophthalmology and the careful legislative watch required to monitor attempts by non-physicians to persuade legislators that they are competent to practice medicine and surgery. Paul Lichter told of the programs of the American Medical Association and the mechanisms for introducing resolutions for consideration by the House of Delegates. Joel Sacks described the activities of the American Association of Medical

Colleges and emphasized the need for department chairmen to be familiar with affirmative action programs.

Robert Kalina described the variations in the time and depth of ophthalmology training provided medical students at different medical schools. Henry Metz described the differing requirements in Medicaid and Medicare regulations in various states. George Weinstein told of the AUPO placement service by which the names of potential academicians are distributed to its members. Dr. Kalina told of the compensation structures at different universities with details reserved for those who participated in the survey. John R. Lynn described the wide variation in the number of full-time and part-time faculty members in various departments. There appear to be 596 full-time M.D.s and 225 full-time Ph.Ds in the various medical schools.

Malcom Luxenberg discussed graduate education programs for residents and fellows. There was general agreement that fellowship programs did not impair the quality of residency training. David Paton, Mr. David Weeks, and Mr. William Murphy discussed fund raising with emphasis on the importance of the individual physician explaining the needs and the rewards to interested patients. Thomas Pettit indicated that every ophthalmic training program in the country participated in the Ophthalmic Knowledge Assessment Program (OKAP). David Worthen discussed manpower in ophthalmology. With some 400 to 500 physicians finishing ophthalmic training annually and more ophthalmologists practicing longer than ever before, the number of ophthalmologists in active practice is steadily growing.

Herbert E. Kaufman succeeds Dr. Reinecke as president for the term ending in 1981 after the annual meeting. Robert Kalina was elected trustee for the class of 1985 and Thomas Acers for 1986.

FRANK W. NEWELL

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THE OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM ITS FIRST HUNDRED YEARS

In February 1880 a small group of physicians interested in diseases of the eye met in London at the home of Mr. William Bowman to consider the founding of a society of ophthalmologists from the three Kingdoms and Ireland. Although the names of those who attended this initial meeting are not available, most certainly its members included Jonathan Hutchinson, the most famous general practitioner in the world; Hughlings Jackson, the neurologist; and John W. Hulke, an ophthalmologist who was famous as a paleontologist. Each was destined to follow Bowman as president of the Society.

The letter of invitation that was sent announcing this first meeting stated that:

> In considering the best means for fostering work, encouraging discussion, and facilitating publication in ophthalmology, it must not be forgotten that communications in this department are made every year to the general medical societies, and that a special Ophthalmological Society might be thought by some to be less useful, and meet with less support, than the alternative of a special section of some one of the older societies. This alternative would, it is believed, have fewer advantages than the plan now proposed. Moreover it was, we understand, mooted some years ago without result. It is felt that the sole objection to a separate special society is that it might tend to encourage narrowness and exclusiveness of work. But, on the other hand, a society representing a subject which, like ophthalmology, is closely connected with every branch of medicine and surgery, may hope, by numbering amongst its members those who work at ophthalmic subjects from many different points of view, to avoid degenerating into a mere society of oculists. (Trans. Ophthalmol. Soc. U.K. 1:1, 1881.)

The first organizational meeting of the Ophthalmological Society of the United Kingdom was held on June 23, 1880. Twenty-eight leading ophthalmic surgeons and other interested physicians attended. A list of 50 prospective members' names had been recommended in February and to this list were added the names of 13 additional members. When the first ordinary meeting was held Oct. 28, 1880, there were 141 ordinary members and four honorary members (Helm-

holtz, Donders, Stokes of Cambridge, and Elkenah Williams of Cincinnati). Ordinary meetings were held thereafter on the second Thursday in October, December, January, March, and May, and on the first Thursday in June. An annual general meeting was held on the Friday after the first Thursday in July. Since 1913 only general meetings, lasting two or more consecutive days, have been held annually.

By 1880 organizational ophthalmology was well established in other countries. The International Congress of Ophthalmology had first met in Brussels in 1857. Its ninth meeting was in London under the presidency of Frans Cornelius Donders in 1871. The American Ophthalmological Society, the first national specialty society in the world, was founded in 1864. Soon thereafter, ophthalmic specialty societies were founded in France and Germany.

The delay in the formation of a national ophthalmologic society in the United Kingdom probably resulted from several factors, but mainly from the belief that members of the society should be trained to practice in all phases of medicine and surgery and not solely be limited to the eye. The immediate stimulus for formation of the society may have resulted from the formation of the Section on Ophthalmology within the British Medical Association a year earlier. Additionally, Donders was president of the International Medical Congress, when it met in Amsterdam in 1878, and formed its own eye section. Bowman in turn chaired the session in ophthalmology when this congress met in London in 1881.

The Ophthalmological Society of the United Kingdom is particularly a monument to its founder William Bowman. He was a remarkable scientist and observer, though a reluctant ophthalmologist. He had dreamed of becoming a great surgeon. His accurate description of the anatomy and function of the eye in a monograph in 1844 resulted in a concentration of patients with ophthalmic disorders, and his dream was thwarted. He was easily Great Britain's most distinguished eye specialist. He first used chloroform for general anesthesia for cataract extraction in 1847 and he was responsible for many innovations in ophthalmic surgery extending far beyond the development of the Bowman probes for lacrimal dilation. He was a man of his time: He learned ophthalmoscopy from Helmholtz at the time of the Great Exhibition in London in 1851. He was an intimate friend of Donders and von Graefe, and corresponded widely with Darwin. (Donders had anticipated Darwin's theory of evolution in a monograph in 1848, a precedent that Darwin freely acknowledged.) Bowman worked with Florence Nightingale before Crimea and was responsible for the introduction of nurses in the King's College Hospital of London. Even after his retirement he was active, attracting Joseph Lister from Edinburgh to the chair of surgery at King's College.

Upon Bowman's retirement as president of the Ophthalmological Society in 1883 the Bowman Lecture was established. This Lecture has been an annual event of the Society and it has become one of the most prestigious lectures in medicine, given by the world leaders in ophthalmology and the geniuses of British medicine: Hutchinson, Leber, Snellen, Fuchs, Morax, van der Hoeve, Weve, and Dale to name just a few of the major contributors. The 1980 Bowman Lecture will be given by Lorenz Zimmerman.

The Society commemorates the name of Treacher Collins with a prize awarded each three years for the best essay submitted on a subject selected by the Council. The Nettleship prize is awarded to a British subject for the most valuable contribution to ophthalmology during the three years immediately preceding

or since the last award, or for the best work done on any subject selected by the Council.

The hundred years since the founding of the Society have seen a flowering of ophthalmology with singular contributions by members of the Society. Their names constitute a litany of ophthalmic luminaries: Argyll Robertson, Ballantyne, Batten, Coats, Collins, Doyne, Duke-Elder, Eales, Elliott, Gunn, Guthrie, Gower, Holmes, Hudson, Hulke, Hutchinson, Jackson, Johnson, Maddox, Mayou, Moore, Mooren, Nettleship, Parsons, Smith, Stallard, Stevens, Swanzy, Tay, Thomas, Traquair, Usher.

Some 15 ophthalmic societies in Great Britain and former countries of the British Empire have affiliated with the Ophthalmological Society of the United Kingdom. Its Transactions, issued annually between 1881 and 1974, has become the Transactions of the Ophthalmological Societies of the United Kingdom and it is now issued quarterly. It is consistently one of the most useful journals available to the clinician.

As the Ophthalmological Society of the United Kingdom begins its second century, the members of the Editorial Board of THE AMERICAN JOURNAL OF OPHTHALMOLOGY join with their colleagues throughout the world in wishing the Society a second century as richly rewarding as the first.

FRANK W. NEWELL

CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Laser Radiation Absorbed by the Retinal Pigment Epithelium

Editor:

The accepted model of laser radiation damage to the paramacular retina relates the extent of damage mainly to the amount of radiation absorbed by the retinal pigment epithelium[1-3] and less to radiation absorbed by the choroidal pigment. An analytic model developed by Wheeler[4] indicates that the contribution of the choroid to retinal temperature increase becomes even less significant as the image diameter grows smaller and the pulse duration shortens.

Several articles published in the last two decades state that darkly pigmented fundi are more susceptible to laser radiation than lightly pigmented ones.[3,5] The logic underlying this statement is that in darker fundi the retinal pigment epithelium contains a greater concentration of melanin granules than the retinal pigment epithelium in lighter fundi, with more light radiation absorbed under similar conditions and more extensive damage inflicted to the retina.

In general ophthalmologists find that fundi of people with fair skin seem to be less pigmented than fundi of darker people. This may lead to the conclusion that blacks are more susceptible to ocular laser radiation than whites.

In an extensive review of published reports we found only one report relevant to this point, and surprisingly enough the results clearly indicate the above conclusion to be wrong. In their excellent paper published in 1962 Geeraets and associates[6] showed that the sum of light radiation absorbed by the retinal pigment epithelium and choroidal melanin pigment in blacks is indeed higher than in white people. However, they clearly demonstrated that in blacks most of the radiation was absorbed in the choroid, the amount absorbed by their retinal pigment epithelium being significantly smaller than that absorbed by the retinal pigment epithelium in whites.

This puts white people at a greater risk of damage from visible laser radiation even though their fundi appear to be less pigmented than those of blacks.

This unique observation has not received its due consideration in published reports on laser safety to date, even though it may have significant implications upon the establishment of laser safety criteria for different races. Much research is required to clarify this issue further.

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AND
ELISHA BARTOV, M.D.
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Inexpensive Support for Anterior Segment Photography

Editor:

Photography of the anterior segment requires a sturdy and adjustable support for the patient's head and the camera, combined with a movable light source. To satisfy these requirements, I modified a Zeiss slit-lamp table so that it would securely support both a 35-mm camera and an electronic flash unit (Figure). The camera support, made from steel shelving, holds the camera with a tripod screw 39 cm above the table surface. The support was screwed to the Zeiss table 6 cm from the rear edge to provide an adequate focusing range with the lens used. The flexible neck from a gooseneck lamp was attached to the forehead support of the slit-lamp table and the electronic flash unit was attached to the free end of the flexible arm. Another tripod screw allowed movement through a 180-degree arc. This arrangement of camera and flash allows correct positioning of the light source and precise focusing of the camera by adjustment of the controls of the slit-lamp table.

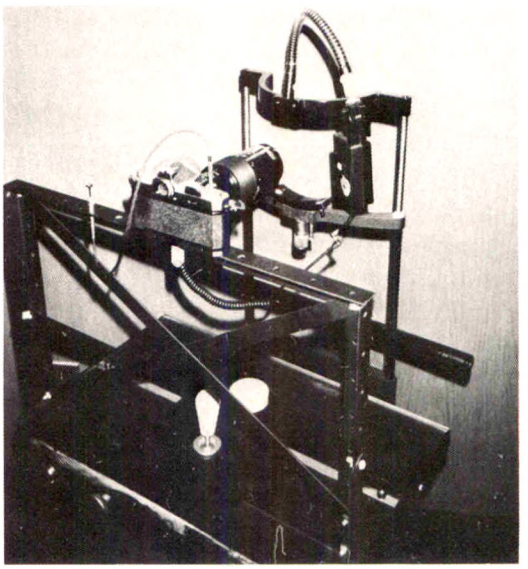

Figure (Brown). Camera and flash mounted on Zeiss table.

ALAN C. BROWN, M.D.
New York, New York

Three Cases of Dendritic Herpetic Ulcerations of the Conjunctiva

Editor:

The dendritic figure in the corneal epithelium is diagnostic of acute herpes simplex keratitis; however, the morphogenesis of this branching lesion has not been clearly defined.[1] Dendritic ulcerations of the conjunctiva, on the other hand, have rarely been reported,[2] and we therefore describe three patients with

ocular herpes simplex who had dendritic conjunctival ulcerations.

Case reports

Case 1—A 64-year-old man with a carcinoma of the lung was seen because of complaints of photophobia and tearing of the right eye for two days. Slit-lamp examination showed superficial punctate erosions and two dendritic ulcerations of the inferior bulbar conjunctiva, which stained with fluorescein. The next day several dendritic ulcerations appeared on the cornea. Herpes simplex virus type 1 was isolated from the conjunctival ulcerations.

Case 2—A 42-year-old man was treated with subconjunctival injections of corticosteroids because of anterior uveitis. He had had previous attacks of herpetic dendritic corneal ulcerations. Five days after the corticosteroid injection a dendritic ulcer appeared on the conjunctiva. The corneal epithelium was normal. The treatment was then stopped and the cornea remained normal and the conjunctival ulceration cleared in three days.

Case 3—A 29-year-old man was seen because of a recurrence of ocular herpes with dendritic ulceration of the cornea. Examination of the conjunctiva showed two dendritic ulcers on the bulbar conjunctiva. The isolate was herpes simplex virus type 1.

Brown and associates[3] and Darougar and associates[4] described herpes simplex conjunctivitis but they did not mention dendritic ulceration. Laibson[2] noted such dendritic figures of the conjunctiva. In Case 1, the conjunctival dendritic figure led to the diagnosis of ocular herpes before corneal imvolvement. This case emphasizes the importance of conjunctival examination. Some investigators have suggested there is a particular structure to the corneal epithelium that makes it specifically susceptible to dendritic ulceration. The conjunctival lesions described here would tend to refute this hypothesis.

Joseph Colin, Alain LeGrignou,
Georges Baikoff,
and
Claude Chastel
Brest, France

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Blepharitis and Secondary Conjunctivitis

Editor:

I am not sure whether this is a problem only in this area, but one of the cosmetic purveyors is currently promoting something called "Oil of Olay," which, I presume, is some sort of grease. Since the advertising industry has persuaded many of my patients to use this product, there has been an increase in blepharitis and secondary conjunctivitis, as well as an increase in the prevalence of demodex. The diagnosis of this condition is easy: the skin is greasy to the touch and the eyelid rims are highly inflamed.

Jerry Hart Jacobson, M.D.
Ogdensburg, New York

Fusarium solani Endophthalmitis

Editor:

In the article, "*Fusarium solani* endophthalmitis without primary corneal involvement" (Am. J. Ophthalmol. 88:764, 1979), by T.W. Lieberman, A. P. Ferry, and E. J. Bottone, the authors believe they are reporting the first case of endogenous mycotic endophthalmitis to occur in a healthy, immunologically competent host. It is well known that fungal infections were a rarity until the widespread use of corticosteroids and glucocorticoid impairment of host defenses. It seems likely that this *Fusarium* oculomycosis was merely an opportunis-

tic infection secondary to 16 days of high-dose systemic, topical, and subconjunctival corticosteroid therapy of antecedent uveitis.

LINAS A. SIDRYS, M.D.
Chicago, Illinois

BOOK REVIEWS

Binocular Vision and Ocular Motility Theory and Management of Strabismus, 2nd ed. By Gunter K. von Noorden. St. Louis, C. V. Mosby Co., 1979. Hardcover, 502 pages, preface, table of contents, index, 461 black and white figures. $57.50

Binocular Vision and Ocular Motility Theory and Management of Strabismus, remains the authoritative volume in the field of strabismus. In the second edition, the contributions of the late Hermann Burian have been essentially unchanged. This seems appropriate both because the subject matter is less prone to change and update, and because Dr. Burian's comments and accounts constitute a direct link with the past, since he worked with many of those who were instrumental in founding the science of strabismology.

The first part of the book offers a thorough, readable account of the anatomy and physiology of the eye as it relates to an understanding of strabismus and amblyopia. The second section of the book contains a thorough discussion of the classification of strabismus and examination techniques. Newer tests such as the random dot stereogram are described and an update is provided on animal models in the investigation of amblyopia. In the third part of the book specific types of strabismus are described and treatment options are outlined. Newer entities such as the nystagmus blockage syndrome are introduced. Dr. von Noorden assumes responsibility for revisions made in all parts of the book, he is even handed in his approach to the subject, but his preferences do come through. In areas such as the timing of surgery for congenital esotropia, for example, he takes a middle ground, not endorsing surgery before 12 months but urging that it be done within the first two years of life.

The fourth section on therapy is a rational approach to both nonsurgical and surgical treatment. A useful series of drawings clearly demonstrates both the commonly performed surgical techniques, and newer techniques such as retroequatorial myopexy, eye muscle transfers and their complications, and shifting of the insertion of the superior oblique tendon for treatment of torsional anomalies.

This volume's chief value is that it provides a complete coverage of a complex subject, presenting a unified, well thought out point of view while at the same time giving the reader a cross-section of the thinking of others. No attempt is made to provide the reader with a predigested meal. Instead, the reader is shown clearly Dr. von Noorden's preference, but allowed to make choices for himself. The exhaustive bibliography includes more than 1,500 references, which reflects Dr. von Noorden's integrity as a scholar and his generosity in crediting others. This book is a must for the ophthalmologist who deals with strabismus.

EUGENE M. HELVESTON

Ophthalmic Plastic and Orbital Surgery. By Michael A. Callahan and Alston Callahan. Birmingham, Aesculapius, 1979. Hardcover, 230 pages, preface, table of contents, reference index, subject index, 75 color figures. $100

This is a well-written, beautifully illustrated book on oculoplastic surgery. Its most outstanding aspect, the numerous

colored illustrations, are consistent in quality. They appear to be three-dimensional, and they demonstrate the surgical concepts and steps accurately.

The chapters on trauma, eyelid reconstruction, and fundamentals of ophthalmic plastic surgery are the best I have ever read on these subjects. The sections dealing with entropion, ectropion, lacrimal surgery, blepharospasm, and the soft tissue socket are also excellent. These sections are well illustrated and they offer a variety of alterative techniques; surgical complications are thoroughly described; and each chapter is adequately referenced and geared to the general ophthalmologist. The chapter on fundamentals of ophthalmic plastic surgery is unique in its extensive description of various oculoplastic techniques including flaps, suturing, anesthesia, and grafting. A description of lacrimal probing and Silastic intubation of the lacrimal system has never been presented so carefully and extensively. The surgical steps in performing a dacryocystorhinostomy and conjunctival dacryocystorhinostomy are difficult to illustrate accurately, but they are superbly depicted here.

In contrast, the chapters on endocrine ophthalmopathy, blepharoptosis, orbital tumors, and conjunctival surgery are somewhat weaker. Illustrations and alternative techniques are fewer. For example, "Surgery For Endocrine Ophthalmopathy" has only four illustrations to explain the surgical steps of eyelid retraction and orbital decompression surgery.

The book emphasizes the authors' recommendations for various oculoplastic surgical techniques. Pre- and postoperative photographs and documentation to prove that the preferred techniques are better than alternative methods are lacking. Also, alternative operations are frequently omitted. Skin grafts for exenteration are recommended, but a popular alternative, which allows the orbit to granulate spontaneously, is not mentioned. Additionally, the authors state that tissue diagnosis is essential when an orbital lesion is located by orbital evaluation, but no mention is made of considering a corticosteroid trial when an inflammatory tumor is diagnosed by A-scan ultrasonography. Moreover, the authors do not differentiate the treatment of paralytic from cosmetic brow blepharoptosis in their description of brow elevation, and they do not describe the popular supratarsal fixation suturing technique to form eyelid creases in conjunction with cosmetic blepharoplasty. One other irritation is that the references listed at the end of each chapter are not consistently cited in the text, which makes it difficult to coordinate material.

Despite these minor criticism, I consider this textbook to be one of the best available on the subject of oculoplastic surgery. The authors provide a great service to the reader by indicating where suture material, needles, and various devices can be obtained. I highly recommend this book as an oculoplastic surgery reference text. The illustrations alone make it worth purchasing.

ALLEN M. PUTTERMAN

The Retinoscopy Book. A Manual for Beginners. By John M. Corboy. Thorofare, New Jersey, Charles B. Slack, Inc., 1979. Paperbound, 143 pages, preface, foreword, table of contents, appendix, index, 123 black and white figures. $9.50

John M. Corboy of the University of Hawaii School of Medicine has written an informative and inexpensive retinoscopy text intended specifically for beginners. Appropriately, he dedicated the book to Jack Copeland, the father of modern retinoscopy, who contributed greatly to the development of streak retinoscopy.

The author organized the book into ten chapters. In the first few chapters he

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Archives of Ophthalmology

CHOROIDAL MELANOMA: ENUCLEATION OR OBSERVATION? A NEW APPROACH. Manschot, W. A., and van Peperzeel, H. A. (Inst. Pathol., Erasmus Univ., Rotterdam, Netherlands). Arch. Ophthalmol. 98:71, 1980.

Application of the knowledge of growth rate of malignant neoplasms on choroidal melanomas shows that (1) fatalities within two years after enucleation only exceptionally can be due to dissemination of tumor cells during enucleation because the growth rate of uveal melanomas generally is far too low; (2) the apparent relationship between enucleation and death by metastasis actually is a relationship in time between diagnosis of the primary tumor and death by metastasis; (3) simultaneous diagnosis of the primary tumor and its metastases rarely is possible; (4) long intervals between enucleation and death by metastasis are explained by a low growth rate of metastases. Early enucleation, especially of small melanomas, is obligatory, because it prevents (further) dissemination of tumor cells. Preoperative local radiotherapy of two doses of 400 rads each will devitalize about 90% of the primary cells and largely will prevent possible iatrogenic dissemination. (5 figures, 2 tables, 45 references) — Authors' abstract

TUMORS OF THE ANTERIOR UVEA. I. METASTASIZING MALIGNANT MELANOMA OF THE IRIS. Sunba, M. S. N., Rahi, A. H. S., and Morgan, G. (Dept. Pathol., Inst. Ophthalmol., London). Arch. Ophthalmol. 98:82, 1980.

Although metastases from malignant melanomas of the ciliary body and choroid are common, similar tumors from the iris are rare. In this article seven such cases are described. They represent 3.5% of 196 cases in the authors files that were followed up for a minimum of five years where the tumor was confined to the iris and did not involve the ciliary body or the choroid. To the authors knowledge, this is the largest series to be described in the literature. Of the seven patients who died of metastases, six were male and autopsies were performed on four. There is evidence that diffusely infiltrating, heavily pigmented tumors, and tumors whose cell nuclei show prominent nucleoli are those most likely to metastasize. (7 figures, 35 references) — Authors' abstract

TRAUMATIC HYPHEMA. FAILURE OF STEROIDS TO ALTER ITS COURSE: A DOUBLE-BLIND PROSPECTIVE STUDY. Spoor, T. C., Hammer, M., and Belloso, H. (Univ. South Carolina; Univ. Rochester; and New York Eye and Ear Infirm., New York, N.Y.). Arch. Ophthalmol. 98:116, 1980.

Forty-three patients with traumatic hyphema were studied prospectively in a controlled, double-blind study. Twenty-three patients received prednisone and 20 received a lactose placebo. Secondary hemorrhages occurred in 16% of all patients. There was no significant difference in the incidence of secondary hemorrhage between the two groups ($P = .85$). There is no evidence that prednisone (40 mg/day) decreases the incidence of secondary hemorrhage. There was no significant difference in final visual acuities between the two groups. Patients with initially larger hyphemas do not appear to have worse final visual acuities. Hyphemas without secondary hemorrhage had a uniformly good prognosis. Although final visual acuities were worse in eyes with secondary hemorrhage, associated ocular injuries rather than blood-related complications accounted for the decreased visual acuity. (5 tables, 19 references) — Authors' abstract

Brain

LEBER'S OPTIC NEUROPATHY: A CLINICAL AND VISUAL EVOKED POTENTIAL STUDY OF AFFECTED AND ASYMPTOMATIC MEMBERS OF A SIX GENERATION FAMILY. Carroll, W. M., and Mastaglia, F. L. (Depts. Med., and Neurol.,

Queen Elizabeth II Med. Ctr., Nedlands, Australia). Brain 102:559, 1979.

Leber's disease is a familial form of optic neuropathy which predominantly affects young males resulting in eventual bilateral optic atrophy. The mode of inheritance is difficult to establish and cannot be accounted for on the basis of an X-linked recessive transmission since females are affected and transmit the carrier state to their daughters. It is possible that transmission is by non-chromosomal means perhaps involving the transfer of a slow virus-like agent. In the current study 14 clinically affected and 40 asymptomatic members in a six-generation family were studied clinically and by recording of visual evoked potentials. Of the 14 affected members, 12 were bilateral and 2 monocular. As might be expected in cases with advanced visual impairment the visual evoked potential was absent bilaterally while in those with less severe involvement responses which were delayed, desynchronized and much smaller than normal could be recorded. The visual evoked potential findings in clinically affected subjects are in keeping with the severe demyelinating lesion of the optic nerve.

Mild impairment of the color vision, pallor of the optic nerve head and/or mild abnormalities or atypical features of the visual evoked potential were found in 16 of the 40 asymptomatic family members studied. Such abnormalities were present in 50 percent of descendants from the female lineage who were at risk of developing the disease, and also in 30 percent of descendents from male lineages who were not at risk. These findings suggest that there is a stage prior to the onset of visual impairment during which subtle abnormalities may be detected in individuals at risk of developing or transmitting the disease. The finding of asymptomatic abnormalities in descendants from male lineages could be accounted for by transmission of a partial form of the disease by affected or unaffected males, which would be in accord with a cytoplasmic mechanism of transmission for the disease. (9 figures, 4 tables, 38 references) — David Shoch

British Journal of Ophthalmology

ACUTE CLOSED-ANGLE GLAUCOMA: AN INVESTIGATION INTO THE EFFECT OF DELAY IN TREATMENT. Hillman, J. S. (St. James's Univ. Hosp., Leeds). Br. J. Ophthalmol. 63:817, 1979.

A retrospective study of 212 eyes with acute closed-angle glaucoma is reported. A peak incidence in the sixth decade was noted and an increased incidence in females confirmed statistically. A surprising and often marked delay occurred in the presentation of many patients for treatment, but visual outcome was not influenced by such delay. Despite good control of intraocular pressure, many of the eyes suffered visual loss from optic nerve damage, and the visual outcome was not related to the height of intraocular pressure at presentation. Damage to the visual system occurred very early in the disease, probably with the initial acute rise of intraocular pressure, and eyes appear to vary in their susceptibility to such an insult. It does not appear that earlier presentation of the patient with acute glaucoma would significantly improve the visual outcome in terms of visual acuity. The short critical time before damage occurs to the eye suggests a role for preventive ophthalmology in the detection and surgery of eyes at risk with shallow anterior chambers and narrow angles before they develop acute closed-angle glaucoma. (7 figures, 5 tables, 10 references) — Author's abstract

OCULAR INVOLVEMENT IN SCLERODERMA. West, R. H., and Barnett, A. J. (Alfred Hosp., Melbourne, Australia). Br. J. Ophthalmol. 63:845, 1979.

Thirty-eight patients with scleroderma (progressive systemic sclerosis) without renal failure were subjected to detailed clinical ophthalmic assessment. Abnormalities were frequent but many of them were age-related and those that can be ascribed specifically to scleroderma include telangiectasia and dermal sclerosis of the eyelids, a tearing defect of varying severity, injection, telangiectasia and sludging of the blood column in conjunctival vessels and perhaps punctate defects of the iris pigment epithelium. (10 references) — David Shoch

Henry Ford Hospital Medical Journal

ISOLATION OF AN ACID-FAST ORGANISM FROM THE AQUEOUS HUMOR IN A CASE OF SARCOIDOSIS. Barth, C. L., Judge, M. S., Mattman, L. H., and Hessburg,

P. C. (Dept. Pathol., Henry Ford Hosp., Detroit, Mich.). Henry Ford Hosp. Med. J. 27:127, 1979.

The anterior chamber fluid from the eye of this patient with sarcoidosis was found to contain microcolonies of a cellwall-deficient organism that was propagated and identified as acid-fast by the Intensified Acid-Fast stain. The colonies were inoculated into mice and retrieved from the dead or sacrificed animals. This report suggests that the acid-fast microbe in the aqueous humor of this case of uveitis-sarcoidosis may be the same organism as that found in the blood in sarcoidosis. Thus, it may be associated not only with the primary disease, but also with the complications of Boeck's sarcoidosis. (8 figures, 20 references) — Authors' abstract

Human Genetics

GENETICS OF RETINOBLASTOMA. Vogel, F. (Inst. Anthropologie und Humangenetik, Univ. Heidelberg, Heidelberg, Germany). Hum. Genet. 52:1, 1979.

This very extensive review of the genetics of retinoblastoma summarizes the voluminous literature on the subject. The following conclusions may be drawn. The mode of inheritance of the hereditary variety is autosomal dominant with about a 90% penetrance. About 68% of inherited cases are bilateral, about 32% unilateral. The vast majority of all patients are sporadic cases, that is they are the only affected members in the family. However, the proportion of bilateral cases is much lower among sporadic than among hereditary cases. All bilaterally affected patients with sporadic retinoblastoma and patients with unilateral sporadic retinoblastoma with more than one primary tumor have to be regarded as germ cell mutants. They will transmit the gene to 50% of their offspring. About 10% of unilateral sporadic cases are germ cell mutants and the rest are not hereditary. In these cases the tumor is probably caused by somatic mutation. In a minority of cases, a chromosomal anomaly has been observed. Generally, this is a deletion of the long arm of chromosome 13. In addition to retinoblastoma these patients show a variable degree of general or mental retardation. In general, patients with hereditary retinoblastoma run an increased risk of becoming affected with other tumor diseases such as osseous sarcomas in later life. As a consequence of improved survival and reproduction of retinoblastoma patients an increase in the incidence of this disease and in the proportion of bilateral cases among all retinoblastoma patients must be anticipated. (6 figures, 18 tables, 144 references) — David Shoch

Investigative Ophthalmology and Visual Science

INCREASE IN AXIAL LENGTH OF THE MACAQUE MONKEY EYE AFTER CORNEAL OPACIFICATION. Wiesel, T. N., and Raviola, E. (Depts. Neurobiol., and Anat., Harvard Med. School, Boston, Mass.). Invest. Ophthalmol. Vis. Sci. 18:1232, 1979.

The cornea of one eye was opacified in two young macaque monkeys by multiple stromal injections of a suspension of polystyrene particles (latex). Ultrasound measurements showed that the eye with the opaque cornea grew at a faster rate, so that after one year it was more than 1 mm longer than the normal eye. This difference in axial length was due to elongation of the posterior segment, since lens thickness, depth of anterior chamber, and corneal curvature were identical in both eyes. At histological examination, no pathological changes were observed in the anterior segment of the latex-injected eye except for a scant vascularization of the corneal opacity. The result of this experiment demonstrates that opacification of the cornea has effects on axial length similar to, although less marked than, those on eyelid fusion and therefore supports the authors previous conclusion that the myopia caused by eyelid fusion is triggered by the abnormal visual input and involves central visual pathways. (3 figures, 2 tables, 13 references) — Authors' abstract

Journal of Neurology, Neurosurgery and Psychiatry

THE AFFERENT PUPILLARY DEFECT IN ACUTE OPTIC NEURITIS. Ellis, C. J. K. (Dept. Med. Ophthalmol., St. Thomas' Hosp., London). J. Neurol., Neurosurg., Psychiatry 42:1008, 1979.

Twenty-two patients with acute optic neuritis were studied by the techniques of infrared pupillometry and visual evoked responses to pattern reversal. A relative afferent pupillary defect was found in all cases and the magnitude of this defect was found to be related to the amplitude, but not to the latency, of the visual evoked responses. During follow-up the afferent defect was found to remain persistently abnormal while other methods of clinical evaluation could not demonstrate abnormality reliably. The amplitude of the visual evoked responses also remained low. (9 figures, 23 references) — Author's abstract

Journal of Neurosurgery

INTERNUCLEAR OPHTHALMOPLEGIA FOLLOWING HEAD INJURY. Baker, R. S. (Dept. Neurol., Univ. Kentucky Med. Ctr., Lexington, Ky.). J. Neurosurg. 51:552, 1979.

Generally internuclear ophthalmoplegia is thought to be almost characteristic of multiple sclerosis. When this has been ruled out the second most common cause is vascular disease of the brain stem. It is important to realize that the other etiologies have been listed as well. These include tumor, Arnold-Chiari malformation, syphilis, myasthenia gravis and head trauma. These should all be considered in the differential diagnosis of internuclear ophthalmoplegia. A patient with this motility abnormality is described where the ophthalmoplegia was transient following head trauma. (1 table, 17 references) — David Shoch

Journal of Pediatric Ophthalmology and Strabismus

PREVIOUS STRABISMUS SURGERY AND EYE POSITION UNDER ANESTHESIA. Owens, P. L., Folk, E. R., and Chen, F. (Dept. Ophthalmol., Eye and Ear Infirm., Univ. Illinois, Chicago, Il.). J. Pediatr. Ophthalmol. Strabismus 16:313, 1979.

The authors studied eye postition under general anesthesia in 51 patients with concomitant esotropia or exotropia, divided into two groups. One group consisted of strabismus patients who had had no previous surgery. The second group consisted of strabismus patients who had undergone previous surgery on one (asymmetric) or both (symmetric) eyes. They found that both groups showed either no change or more divergence under general anesthesia in comparison to their preoperative state. Those patients who had had no previous surgery revealed an equal divergence in both eyes. This relationship also held true for those patients who had undergone symmetrical surgery in both eyes. However, those patients who had had surgery in one eye only, showed more divergence in the operated eye than in the unoperated one. These findings reflect the mechanical-anatomical factors created by the surgery itself. (4 tables, 5 references) — Authors' abstract

A NEW RATIONALE FOR THE MANAGEMENT OF LARGE ANGLE ESOTROPIA. Hess, J. B., and Calhoun, J. H. (Wills Eye Hosp., Philadelphia, Pa., and Univ. South Florida, Tampa, Fla.). J. Pediatr. Ophthalmol. Strabismus 16:345, 1979.

In 19 patients with an esotropia ranging from 35-75 prism diopters, 6 mm bilateral medial rectus recessions were performed which resulted in a correction ranging from 35-90 prism diopters with an average of 58. In 10 patients with esotropia ranging from 60-100 prism diopters, 7 mm bilateral medial rectus recessions were performed resulting in a correction ranging from 55-90 prism diopters with an average of 72. The procedures were performed using a fornix approach and without conjunctival recession. No significant limitations of ductions or versions resulted. This method reduced the number of surgical procedures necessary to correct large angle deviations. (4 tables, 15 references) — Paul E. Romano

Klinische Monatsblaetter für Augenheilkunde

BLINDNESS FOLLOWING ORBITAL HEMORRHAGE AFTER HEAD INJURIES. (German) Schnaudigel, O. E., and Doden,

W. (Univ. Eye Clinic, Frankfurt, W. Germany). Klin. Monatsbl. Augenheilkd. 174:387, 1979.

Severe orbital hemorrhage can follow a contusion of the orbit. Deep orbital arterial bleeding can lead to enough intraorbital pressure to cause visual loss and blindness. This emergency is recognized by: livid eyelids with a narrow palpebral fissure which can only be slightly open by active or passive effort; proptosis up to 10 mm with resistance to retropulsion and active and passive immobilization of the eye; elevated intraocular pressure as great as 80mm/Hg; retinal ischemia and visual loss; and general symptoms, including bradycardia, nausea and diaphoresis.

Seventeen cases were seen since 1972. Seven patients were not treated until more than three hours after onset of the tight orbit and had permanent visual loss. Nine patients were treated early by an incision through the skin and orbital septa over the lateral half of the inferior orbital rim. The authors recommend immediate orbital decompression by such an incision whenever vision is threatened by a tight orbit and retinal ischemia. (1 figure, 15 references) — Peter Egbert

SEVERE COMPLICATIONS FOLLOWING THE IMPLANTATION OF ARTIFICIAL LENS. (German) Hamburg, A., and Winkelman, J. E. (Univ. Eye Clinic of Utrecht, Utrecht, Netherlands). Klin. Monatsbl. Augenheilkd. 175:197, 1979.

In the Netherlands, the number of cataract operations with intraocular lens implantation has been increasing in recent years. The ratio of cataract removal without implant to cataract removal with implant is now approximately two to one.

Between 1973 and 1976, the pathology laboratory at Utrecht received 12 eyes which had been enucleated for complications following cataract extraction—six eyes with an intraocular lens (either a Binkhorst iridocapsular or iris clip lens or a Worst Medallion lens). These six eyes with an intraocular lens had the following histopathological findings: all had degeneration of the corneal endothelium; three had total retinal detachment; one had metastatic panophthalmitis; one had a corneal abscess with secondary endophthalmitis; and one had epithelial downgrowth with bullous keratopathy. The authors emphasize that intraocular lens implantation entails a greater risk than conventional cataract operation. (7 figures, 4 tables, 13 references) — Peter Egbert

ABNORMALITIES IN THE VESSELS OF THE IRIS AS SEEN IN FLUORESCEIN ANGIOGRAPHY. (German) Kluxen, G., and Friedburg, D. (Univ. Eye Clinic, Dusseldorf, West Germany). Klin. Monatsbl. Augenheilkd. 175:211, 1979.

Occasionally, unusually thick serpentine vessels which do not leak fluorescein during angiography are found in the iris. These are shunt vessels which run radially from the iris root toward the pupil, course next to the pupillary margin for a short distance, then return to the iris root. Four patients who had such vessels studied by iris angiography five and one-half to seven years ago were restudied and it was found that the abnormal iris vessels had not changed. Three of the eyes had associated disease: Sturge-Weber disease, high myopia and open angle glaucoma. (7 figures, 16 references) — Peter Egbert

Plastic and Reconstructive Surgery

MODIFIED THREE-WALL ORBITAL EXPANSION TO CORRECT PERSISTENT EXOPHTHALMOS OR EXORBITISM. Wolfe, S. A. (Div. Plastic Surg., Univ. Miami, Miami, Fla.). Plast. Reconstr. Surg. 64:448, 1979.

Ordinarily in an attempt to expand the orbital volume, one wall of the orbit is removed. Ophthalmologists tend to remove the lateral wall in a Kronlein procedure, neurosurgeons remove the superior wall or roof via a Naffziger approach and otolaryngologists remove the floor and the medial wall in the procedure of Walsh and Ogura. In rare cases even this does not suffice and a greater expansion of the orbital volume is required. The author describes a procedure that will increase the orbital capacity by more than 100%. This procedure is a modification of one originally described by Tessier in which a greenstick fracture of the anterior part of the zygomatic

arch is made to hinge out the lateral part of the orbit. There is also some posterior displacement of the lateral orbital wall in this procedure. The authors modified this to raise the lateral end of the lower osteotomy line to just above the attachment of the zygomatic arch and this makes it possible to move the lateral orbital wall out without posterior displacement. (6 figures, 1 table, 12 references) —David Shoch

Postgraduate Medical Journal

RECOGNITION AND CHEMOTHERAPY OF OCULOMYCOSIS. Jones, B. R., Clayton, Y. M., and Oji, E. O. (British Postgraduate Medical Federation, Univ. London, London). Postgrad. Med. J. 55:625, 1979.

Oculomycosis may occur as infection of the orbit usually arising from the paranasal sinuses or from trauma, or it may present as an involvement of the globe. The latter is the more common and usually is seen as a corneal infection or post-surgical and post-traumatic fungal endophthalmitis. *Candida* accounts for about 50% of the recorded cases while of the filamentous organisms, *Aspergillus* accounts for about half and a wide variety of other organisms for the remaining cases. *Candida* is best treated with flucytosine combined with either amphotericin B or natamycin. The best treatment at this time for *Aspergillus* appears to be econazole, clotrimazole or miconazole combined with thiabendazole. Natamycin has also been used for filamentous fungal infections but it does not penetrate well and it should not be combined with imidazoles for anti-fungal chemotherapy because of antagonistic drug interactions. The most widely acting of the above drugs appears to be econazole. It must be emphasized, though, that effective treatment depends entirely on accurate identification of the offending organism and since mycotic infections are not clinically very different from other infections a good microbiology laboratory remains the essence of successful therapy of corneal and intraocular infectious processes. (2 figures, 2 tables, 9 references)—David Shoch

Science

STEREOPSIS IN HUMAN INFANTS. Fox, R., Aslin, R. N., Shea, S. L., and Dumais, S. T. (Dept. Psychol., Vanderbilt Univ., Nashville, Tenn., and Dept. Psychol., Indiana Univ., Bloomington, Ind.). Science 207:323, 1980.

Stereoscopic depth perception was tested in human infants by a new method based on attracting the infant's attention through movement of a stereoscopic contour formed from a dynamic random-element sterogram. The results reveal that stereopsis emerges at three and one-half to six months of age, an outcome consistent with evidence for rapid postnatal development of the visual system. (14 references)—Authors' abstract

Virchows Archiv A Pathological Anatomy and Histology

THE TRABECULAR MESHWORK OF A NON-GLAUCOMATOUS EYE WITH THE EXFOLIATION SYNDROME. Benedikt, O., and Roll, P. (Univ. Eye Clin. of Graz, Graz, Austria). Virchows Arch. A Pathol., Anat., and Histol. 384:347, 1979.

Just before enucleation of the eye of a 82-year-old woman for malignant melanoma a trabeculectomy was done. The patient had demonstrated the existence of exfoliation syndrome in both eyes. Her optic nerve heads were normal, there were no field defects and her intraocular pressures had varied between 10 and 14 mm Hg. Immediately after trabeculectomy the specimen was fixed for electron microscopy. The exfoliation material was found mainly in massive deposits in the subendothelial region of the outer and inner wall of Schlemm's canal, in the cribriform area and the uveal meshwork. The concept that the accumulation of exfoliation material is an important pathogenetic factor in the development of glaucoma was not confirmed by this study. (4 figures, 22 references)—David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

Send News Items double-spaced to News Editor, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

ALBANY MEDICAL COLLEGE: LASER IRIDECTOMY COURSE

A one-day instructional course on laser iridectomy will be held at the Department of Ophthalmology, Albany Medical Center, June 5, 1980. The fee is $150. For further information, write the Department of Postgraduate Medicine, Albany Medical College, Albany, NY 12208.

UNIVERSITY OF MICHIGAN MEDICAL SCHOOL: CURRENT PERSPECTIVES IN OPHTHALMOLOGY

The University of Michigan Medical School will hold its spring conference, "Current perspectives in ophthalmology," May 12-14, 1980. For further information, write Dr. Floyd C. Pennington, Director, Office of Continuing Medical Education, Towsley Center for Continuing Medical Education, University of Michigan Medical School, Ann Arbor, MI 48109.

STATE UNIVERSITY OF NEW YORK-KINGS COUNTY HOSPITAL: OPHTHALMOLOGY ALUMNI DAY

The 12th annual Ophthalmology Alumni Day of the State University-Kings County Hospital of Brooklyn, New York will be held on June 5, 1980, at the Downstate Medical Center, Brooklyn, New York. The scientific session will begin at 9 A.M. The Ninth Annual J. Eugene Chalfin Memorial Lecture will be delivered by Joseph Goldstein. There are no fees and all ophthalmologists are invited to attend. For further information, write Mrs. Rita Belsky, State University of New York, Downstate Medical Center, Box 58, 450 Clarkson Ave., Brooklyn, NY 11203.

OHIO STATE UNIVERSITY: SUMMER PROGRAM IN OPHTHALMOLOGY

Ohio State University Department of Ophthalmology and Children's Hospital and Grant's Hospital will sponsor a summer program in ophthalmology, Aug. 17-20, 1980. For further information, write Ms. Anne M. Cooper, Ohio State University, College of Medicine, Center for Continuing Medical Education, A-352 Starling Loving Hall, 320 West Tenth Ave., Columbus, OH 43210.

OHIO STATE UNIVERSITY: EYE UPDATE IN NURSING

Ohio State University Department of Ophthalmology and Ohio State University School of Nursing will sponsor a continuing education course, "Eye update in nursing: developmental views," May 14, 1980. For further information, write Ms. Anne M. Cooper, Ohio State University, College of Medicine, Center for Continuing Medical Education, A-352 Starling Loving Hall, 320 West Tenth Ave., Columbus, OH 43210.

LONG ISLAND JEWISH-HILLSIDE MEDICAL CENTER AND HEALTH SCIENCES CENTER STATE UNIVERSITY OF NEW YORK AT STONY BROOK: CLINICAL DAY

Long Island Jewish-Hillside Medical Center and the Health Sciences Center, State University of New York at Stony Brook, will sponsor a clinical day in ophthalmology, "Retinal vascular disorders," May 14, 1980. The fee is $60. For further information, write Continuing Education Coordinator, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11042.

UNIVERSITY OF SOUTH FLORIDA: PEDIATRIC OPHTHALMOLOGY SEMINAR

The Department of Ophthalmology at the University of South Florida in cooperation with All Children's Hospital, St. Petersburg, will hold a Pediatric Ophthalmology Seminar May 1-3, 1980, at the Don CeSar Resort Hotel on St. Petersburg Beach, Florida. Professor August Deutman of The Netherlands and Robert M. Ellsworth will be the guest speakers. speakers.

AMERICAN ACADEMY OF OPHTHALMOLOGY: 1980 MEETING

The annual meeting of the American Academy of Ophthalmology has been rescheduled for Chicago's McCormick Place on Nov. 2-7, 1980.

SIXTH ANNUAL COLBY COLLEGE OPHTHALMOLOGY SEMINAR

Colby College, in conjunction with Mid-Maine Medical Center, will present a four-day postgraduate seminar, "Disorders of the anterior segment," Aug. 10-14, 1980. For further information, write Robert H. Kany, Director, Special Programs, Colby College, Waterville, ME 04901.

NATIONAL EYE INSTITUTE: NEW APPOINTMENTS

Christina A. Enroth-Cugell, of Evanston, Illinois, James Farmer of Washington, D.C., and Norma F. Krajczar of Morristown, New Jersey, have been

appointed to the National Advisory Eye Council. The Council is the principal advisory body to the National Eye Institute, which is the primary source of support within the Federal Government for research on the eye and visual disorders. As members of the Council, Dr. Enroth-Cugell, Mr. Farmer, and Mrs. Krajczar will advise the National Eye Institute Director and staff on the awarding of grants for vision research and research training. They will also provide guidance on National Eye Institute policy development and program planning.

Hanover, West Germany: Symposium on Cranial Nerves

A symposium on cranial nerves will be held in Hanover, West Germany, June 2-6, 1980. The fee is $400 for physicians and $200 for residents. For further information, write Mrs. I. Fetzer, Neurosurgical Clinic, The City of Hanover, Haltenhoffstrasse 41, 3000 Hanover 1, West Germany.

University of Western Ontario: Annual Clinical Day

The University of Western Ontario, Department of Ophthalmology, Annual Clinical Day will be held May 2, 1980, at University Hospital, London, Ontario. The topic will be "The art and science of refraction."

Presbyterian Hospital of Pacific Medical Center: Highlights of Modern Ophthalmology

Presbyterian Hospital of Pacific Medical Center will present "Highlights of modern ophthalmology," June 19-21, 1980, in San Francisco, California. The fee is $225 for practitioners; $100 for residents. For further information, write Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco, CA 94120.

International Society for Orbital Disorders: Fourth International Symposium on Orbital Disorders

The International Society for Orbital Disorders will sponsor the Fourth International Symposium on Orbital Disorders Aug. 31-Sept. 2, 1981, in Amsterdam. For further information, write J. P.A. Gillissen, M.D., Secretary-General, c/o University Eye Hospital Wilhelmina Gasthuis, le Helmersstraat 104, 1054 EG Amsterdam, Holland.

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American Journal of Ophthalmology

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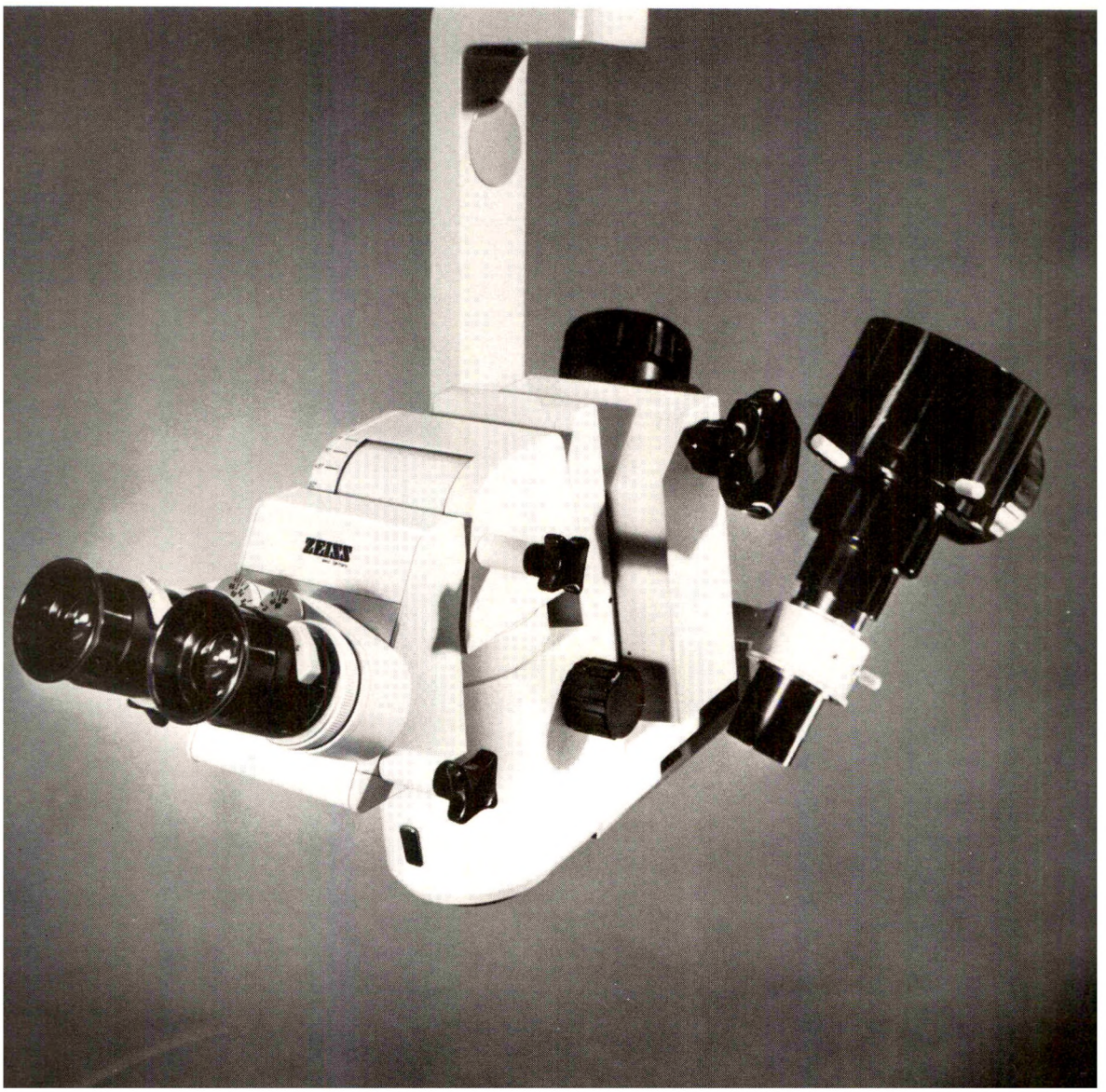

EYE RESEARCH INSTITUTE OF RETINA FOUNDATION AND POSTGRADUATE MEDICAL INSTITUTE

PRESENT

SEVENTH PRACTICAL COURSE ON NEW APPLICATIONS OF VITRECTOMY TECHNIQUES IN THE MANAGEMENT OF ANTERIOR AND POSTERIOR SEGMENT PROBLEMS

MAY 14 and 15, 1980

FACULTY: H. MacKenzie Freeman, M.D., Felipe I. Tolentino, M.D. (Co-Chairmen) Tatsuo Hirose, M.D., J. Wallace McMeel, M.D., I.D. Okamura, M.D., Ronald C. Pruett, M.D., Charles L. Schepens, M.D., Clement L. Trempe, M.D.

GUEST FACULTY: Anton Banko, M.E., Richard Mackool, M.D. Delbert Nachazel, M.D., Richard J. Simmons, M.D.

COURSE DESCRIPTION: This is a combined didactic and practical course on anterior and posterior segment surgery of the eye utilizing advanced vitrectomy instrumentation and techniques. The didactic portion will cover indications, patient work-up, instrumentation, surgical techniques, complications and results. Special emphasis will be given to recent experiences of vitrectomy techniques in trauma, rhegmatogenous retinal detachment, diabetic vitreous hemorrhage and traction retinal detachment, dense pupillary membranes, and congenital as well as traumatic cataracts.

The practical portion of the course involves a closely supervised six-hour session of animal surgery. This course will exclusively feature the M6 System of the Surgical Design Corporation, New York. Participants will have the opportunity to perform closed vitrectomy in animals using "one instrument" and "two instrument" technique. The number of participants is limited.

The Continuing Education Activity, co-sponsored by Postgraduate Medical Institute, is accredited for 15 hours in Category I towards the American Medical Association Physicians' Recognition Award.

INQUIRIES: H. MacKenzie Freeman, M.D.
100 Charles River Plaza
Boston, MA 02114

TUITION FEE: $350.00 Limited Registration.

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ONE DAY INTRAOCULAR LENS COURSE

A practical course emphasizing surgical techniques — Pitfalls and complications

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Course Director Joseph Meltzer, M.D.

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B. Curtin, M.D.
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D. Gormley, M.D.
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CME Credits - 8 Hours - Cat.I

Tuition: $100 Residents $25.00 (includes lunch)

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DEPARTMENT OF OPHTHALMOLOGY

OCTOBER 1, 2, and 3, 1980

ESTELLE DOHENY EYE FOUNDATION

Los Angeles Hilton Hotel—930 Wilshire Boulevard, Los Angeles, 90017

MEDICAL AND SURGICAL MANAGEMENT of INTRAOCULAR INFLAMMATION

This course is designed to aid the practicing ophthalmologist in the diagnosis and medical and surgical management of intraocular inflammation including various uveitis syndromes, endophthalmitis (endogenous and post operative), opportunistic infections in the compromised host, cataract extraction in the uveitis patient, etc. A practical office-oriented approach to the clinical evaluation and laboratory work-up of patients with uveitis will be emphasized, and a detailed description and syllabus describing this approach to diagnosis, work-up, and therapy will be available to all participants.

Discussions of various uveitis syndromes (Toxoplasmosis, Pars Planitis, Candida, Cytomegalic Inclusion Disease, Herpes Simplex and Zoster, Toxocara, J.R.A., etc.) will include diagnostic criteria, natural course, specific therapy, and prognosis. Special attention will be given to the management of complications of ocular inflammation including surgical procedures in the uveitis patient: cataract extraction (indications, techniques, results), glaucoma surgery, reinal detachment procedures, and lensectomy and vitrectomy techniques. Inflammatory complications following I.O.L. insertion will be discussed, including cystoid macular edema.

A special section on the uses and abuses of corticosteroids and the various non-steroidal anti-inflammatory, and immunosuppressive agents will be included as well as a section on complications of these drugs.

The role of special diagnostic studies including ultrasonography, electrophysiology, fluorescein angiography, etc. will be discussed. A special feature will be the "Participating Workshops" in fluorescein angiography, ultrasonography, electrophysiology, and clinical pathologic correlations.

The Estelle Doheny Memorial Lecture .....Herbert E. Kaufman, M.D.
A. Ray and Wendell C. Irvine Memorial Lecture .....G. Richard O'Connor, M.D.

GUEST FACULTY

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Rudolph M. Franklin, M.D.
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Stephen J. Ryan, M.D.
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Tuition: $250.00 (includes syllabus, luncheons, mixers)
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CONFERENCE DIRECTOR: Ronald E. Smith, M.D.

For Application/Brochure: Bill Dowey, Conference Office,
Estelle Doheny Eye Foundation,
1355 San Pablo St.
Los Angeles, CA 90033

PLANNED EXTRACAPSULAR CATARACT EXTRACTION
and
INTRAOCULAR LENS IMPLANTATION WORKSHOP

June 13 and 14, 1980

Twelve Oaks Hospital
Houston, Texas

Faculty:

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William M. Aden, M.D.
Jared M. Emery, M.D.
Johnny Justice, F.O.P.S.
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Lawrence A. Wright, M.D.

Intraocular lenses have become an increasingly attractive alternative means of optical correction for the patient requiring cataract surgery. Planned Extracapsular Cataract Extraction is a controlled technique for the performance of cataract surgery and ideally prepares the eye for intraocular lens implantation. Therefore, the goal of this workshop is to teach the ophthalmic micro-surgeon extracapsular surgery combined with intraocular lens implantation.

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FOR REGISTRATION INFORMATION CONTACT:

Pamela H. Britain
c/o Guy E. Knolle, Jr., M.D.
4126 S.W. Freeway #1700
Houston, Texas 77027
(713) 621-3771

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Content: Basic Physics of Ultrasound, Vitreous and retinal pathology, foreign bodies and ocular trauma, intra-ocular tumors and other mass lesions, ultrasonic measurement of axial length, IOL power calculations.

Course Director: Howard Gilbert, M.D.

Faculty:
Richard Binkhorst, M.D., Stanley Chang, M.D., Yale Fisher, M.D.

$100 Practicing Physicians
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Registration and Information
Contact: Evelyn Peterson
Mount Sinai Hospital
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Minneapolis, MN 55404
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Extension 1117

Approved: 7 hours
Category 1, CME

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St. Paul's Hospital
Vancouver, B.C.

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St. Paul's Hospital is a 550 Acute Care Hospital with an ambulatory care facility and an active Emergency Service.

The duties will include responsibility for the clinical care in the Department of Ophthalmology and supervision of its teaching and research programs.

The position carries a university appointment and appropriate salary support. Private practice on a fee-for-service basis is permitted. Geographic location within the Hospital is expected.

Applications should include curriculum vitae, stating experience including teaching positions held, together with three references.

Applications should be forwarded to:

Dr. Jack Rootman
Chairman, Search Committee for Head of Department of Ophthalmology
% Executive Director
St. Paul's Hospital
1081 Burrard Street
Vancouver, B.C. V6Z 1Y6

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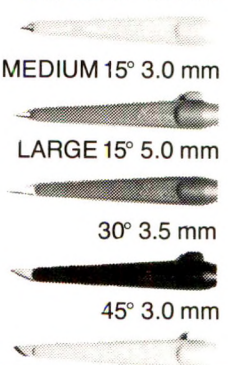

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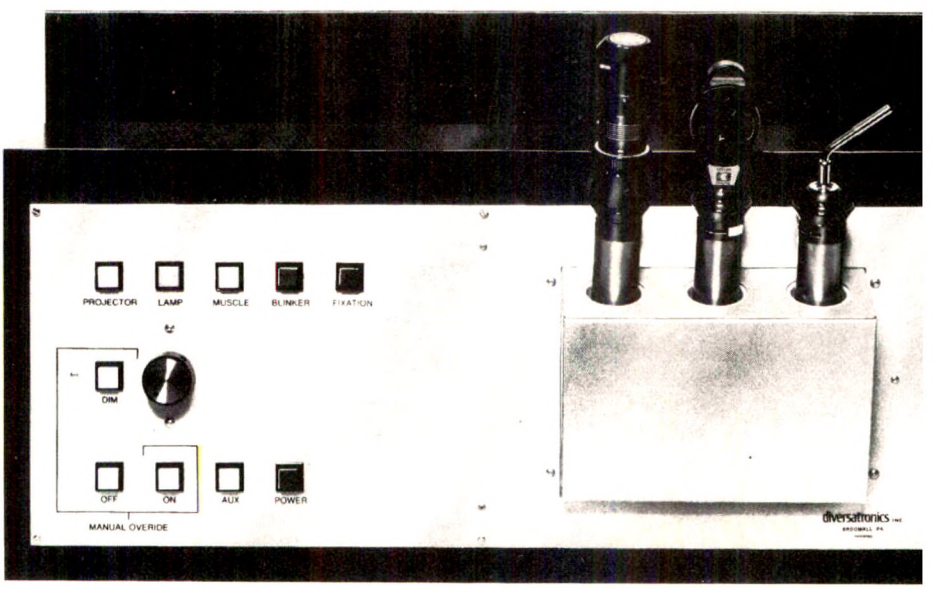

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The National Radial Keratotomy Study Group announces the availability of a practical, two day course in the Radial Keratotomy of Fyodorov. The course will be under the direction of Leo D. Bores, M.D.

Faculty will consist of:

Leo D. Bores, M.D. Course Director
William Myers, M.D. Detroit
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The course will consist of practical demonstrations on animal eyes as well as an opportunity to observe and assist in actual surgery. Slides, tapes, films and lectures in a seminar type of atmosphere will round out the practical and laboratory material. A syllabus will be provided for each participant and discussion tapes (as well as TV cassettes) will be made available.

Enrollment will be strictly limited to experienced microsurgeons and the class size will be kept small to insure adequate personal instruction. Interested applicants should write:

International Foundation for Ophthalmic Research and Education
Suite 106
465 St. Michaels Drive
Santa Fe, New Mexico 87501
and enclose a curriculum vitae
or call: 1-505-988-1874

ANNOUNCEMENT
CALL FOR NOMINATIONS

1980 Award of Merit in Retina Research

The Retina Research Foundation, Houston, Texas, announces a call for nominations for the 1980 AWARD OF MERIT IN RETINA RESEARCH, to recognize a vision scientist whose work represents (a) single outstanding achievement in basic retina research or (b) a potentially significant contribution to new basic knowledge about the retina, its role in the visual process, and/or vitreoretinal diseases and disorders. President and Scientific Director of the Foundation is Alice McPherson, M.D., F.A.C.S., F.I.C.S.

Award: $30,000 (which includes a $1,000 honorarium).

Eligibility: All vision scientists whose research is primarily directed to the retina.

Nomination Procedure: The following must be submitted: (1) letter of nomination including brief statement supporting nominee; (2) brief summary of nominee's achievement or contributions to retina research, plus 3 (maximum) published reprints that best substantiate the work for which he/she is being nominated; and (3) nominee's curriculum vitae including complete bibliography.

Mail completed nominations to: Alice McPherson, M.D., Retina Research Foundation, 6560 Fannin, Suite 2200, Houston, Texas 77030.

Deadline: Nominations must be postmarked no later than June 30, 1980.

Selection and Presentation: The recipient will be selected by a committee of nationally prominent vision scientists and retina specialists appointed by the Foundation. Presentation of the 1980 Award is scheduled in conjunction with the Retina Society's Annual Meeting in Philadelphia, Pennsylvania, October, 1980. The award recipient will be the named lecturer for the Charles L. Schepens Lecture, which is featured in the Retina Society Program.

RRF **RETINA RESEARCH FOUNDATION, HOUSTON, TEXAS**

ALBERT EINSTEIN COLLEGE OF MEDICINE AND MONTEFIORE HOSPITAL
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delivered by
Dr. Alan C. Bird, Professor of Ophthalmology
Moorfields Eye Hospital, London, England
Friday, June 6, 1980

Morning Session: Symposium on Ophthalmic Plastic Surgery
Selected Topics: Orbital Cellulitis • Permeability of Developing Blood-Retinal Barriers • Localization of Elements in Ocular Tissue • Changing Perspectives in Ophthalmic Surgery • Toxic Amblyopia • Automated Perimetry Evolution of Visual Field Defects in Glaucoma • Extended-Wear Contact Lenses • The Physician's Role in the Diagnosis of Specific Language Disability
Afternoon Session: Symposium on Senile Macular Degeneration including Classification and Pathophysiology

Guest Lecturer: Dr. Alan C. Bird • Lecture: DISCIFORM MACULAR DEGENERATION

Participating Faculty of Albert Einstein College of Medicine and Montefiore Hospital and Medical Center include:
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Registration Fee: $50.00 ($25.00 for residents) includes lunch. Registration limited. Make checks payable to George N. Wise Memorial Fund. For registration and further information write to:

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SHEARING INTRAOCULAR LENS COURSE

Techniques of Extracapsular Cataract Surgery

INSTRUCTORS:

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Henry Kell Yang, M.D.—Fellow

3 COURSES—EACH 3 DAYS LONG (LIMITED TO 2 OPHTHALMOLOGISTS FOR EACH COURSE)

May 20th, 21st, 22nd, 1980
June 24th, 25th, 26th, 1980
July 22nd, 23rd, 24th, 1980

Introductory Lectures
Live Surgery—2 days
Cooper Medical Center, Camden, N.J.
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EXTRACAPSULAR CATARACT EXTRACTION
and
INTRAOCULAR LENS IMPLANTATION COURSE

May 3 and 4, 1980

LaPosada Resort Hotel
Scottsdale, Arizona

Course Director: David D. Dulaney, M.D.

Faculty: L. Wayne Freeman, M.D.
Kenneth J. Hoffer, M.D.
Guy E. Knolle, Jr., M.D.
David J. McIntyre, M.D.

This program will include detailed instruction and experience with extra-capsular surgery utilizing animal eyes. Emphasis and instruction will be on automated irrigation/aspiration techniques utilizing Cavitron equipment. Intraocular lens insertion techniques suitable for extracapsular surgery will be demonstrated and practiced with animal and artificial eyes.

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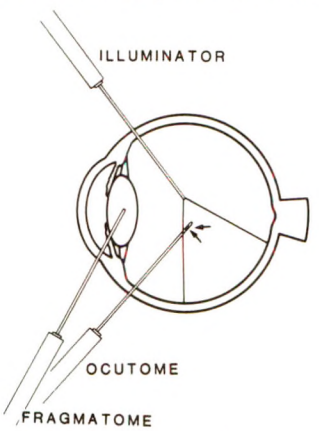

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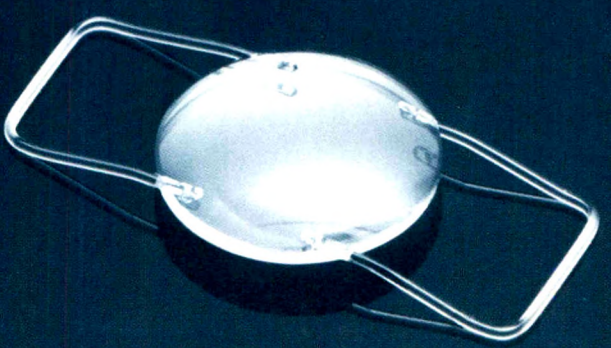

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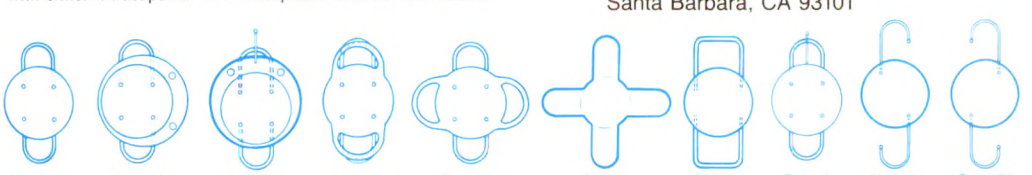

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Contraindicated in narrow angle glaucoma and hypersensitivity. Use with caution in elderly patients with severe cardiovasc disease including arrhythmias; poorly controlled hypertension; and diabetes, especially diabetic ketoacidosis. Avoid contamination of dropper tip. The following adverse reactions may occur: Pupillary dilation, increase in IOP, systemic effects due to absorption (i.e., hypertension, cardiac irregularities and hyperglycemia).

[1]**Alcon Double Masked Studies — Protocol No. 77-1-07**

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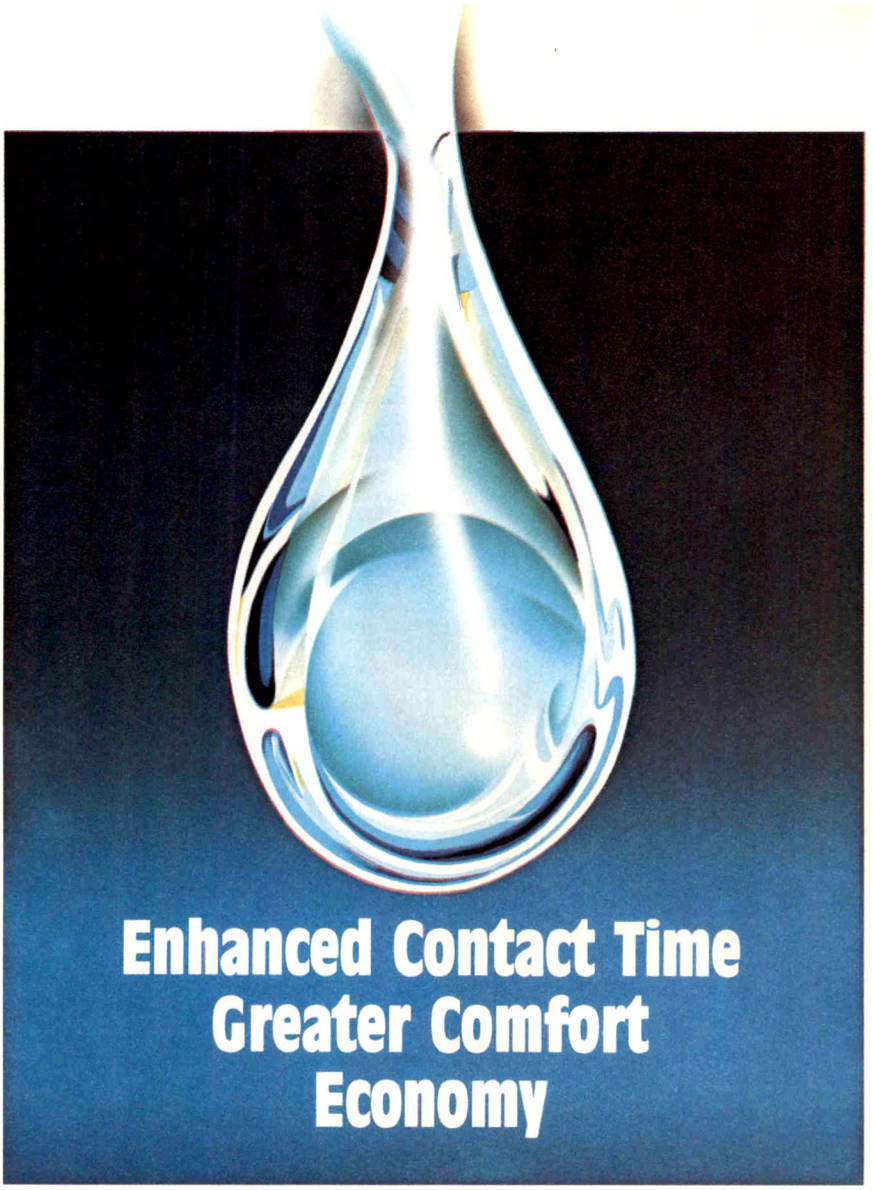

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'TION: A sterile ophthalmic solution and ointment. Each ml of solution contains: Active: phenicol 0.5% (5 mg/ml). Preservative: Thimerosal 0.01%. Vehicle: Hydroxypropyl illulose. Inactive: Boric Acid, Sodium Borate (to adjust pH), Purified Water. Each gram of contains: Active: Chloramphenicol 1.0% (10 mg/g). Inactive: Mineral Oil, Anhydrous Liquid White Petrolatum. CONTRAINDICATIONS: Sensitivity to any component. WARNINGS: corneal wound healing. PRECAUTIONS: Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If new infections appear, discontinue and take appropriate measures. Except for very superficial infections, this drug should be supplemented by appropriate systemic medication. ADVERSE REACTIONS: Blood dyscrasias may be associated with systemic use. One case of bone-marrow hypoplasia following prolonged topical use has been reported. DOSAGE: Solution: 2 drops hourly to four times daily. Ointment: Apply a small amount at bedtime as a supplement to the drops

VIRA-A®
(vidarabine ophthalmic ointment), 3%

Description. Vira-A (vidarabine, adenine arabinoside, or Ara-A) is an antiviral drug for topical ophthalmic administration. The chemical name is 9-β-D-arabinofuranosyladenine. Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

Clinical Pharmacology. Vira-A is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Except for Rhabdovirus and Oncornavirus, Vira-A does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

The antiviral mechanism of action has not been established. Vira-A appears to interfere with the early steps of viral DNA synthesis. Vira-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of Vira-A. Because of the low solubility of Vira-A, trace amounts of both Vira-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of Vira-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, Vira-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, Vira-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit.

Indications and Usage. Vira-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. Vira-A is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions to idoxuridine have occurred. The effectiveness of Vira-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous Vira-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone, have been administered concurrently with Vira-A Ophthalmic Ointment, 3%, without an increase in adverse reactions.

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If Vira-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

Vira-A is not effective against RNA virus or adenoviral ocular infections. Vira-A is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Contraindication. Vira-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. ***Use in Pregnancy:*** Vira-A (vidarabine) parenterally is teratogenic in rats and rabbits. Ten percent Vira-A ointment applied to 10% of the body surface during organogenesis induc fetal abnormalities in rabbits. When 10% Vira-A ointment was a plied to 2 to 3% of the body surface of rabbits, no fetal abn malities were found. This dose greatly exceeds the total recc mended ophthalmic dose in humans. The possibility of embryo or fetal damage in pregnant women receiving Vira-A (vidarab ophthalmic ointment), 3%, is remote. The topical ophthalmic dc is small, and the drug relatively insoluble. Its ocular penetratior very low. However, a safe dose for a human embryo or fetus h not been established. Consequently, Vira-A should be used o when clearly indicated.

It is not known whether Vira-A is excreted in human milk. A general rule, because many drugs are excreted in human m nursing should not be undertaken while a patient is under tre ment. However, excretion of vidarabine in breast milk is unlik because Vira-A is rapidly deaminated in the gastrointestinal tra

Mutagenic Potential: Results of *in vitro* experiments indica that vidarabine can be incorporated into mammalian DNA and c induce mutation in mammalian cells (mouse L5178Y cell lir Thus far, *in vivo* studies have not been as conclusive, but there some evidence (dominant lethal assay in mice) that vidarabi may be capable of producing mutagenic effects in male ge cells.

It has also been reported that vidarabine causes chromoso breaks and gaps when added to human leukocytes *in vitro*. Wh the significance of these effects in terms of mutagenicity is n fully understood, there is a well-known correlation between t ability of various agents to produce such effects and their abil to produce heritable genetic damage.

Oncogenic Potential: Chronic parenteral (IM) studies vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant crease in liver tumor incidence among the vidarabine-treat females. In the same study, some vidarabine-treated male m developed kidney neoplasia. No renal tumors were found in t vehicle-treated control mice or the vidarabine-treated fem mice.

In the rat study, intestinal, testicular, and thyroid neoplasia c curred with greater frequency among the vidarabine-treat animals than in the vehicle-treated controls. The increases thyroid adenoma incidence in the high-dose (50 mg/kg) ma and the low-dose (30 mg/kg) females were statistically sign cant.

Hepatic megalocytosis, associated with vidarabine treatme has been found in short- and long-term rodent (rat and mou studies. It is not clear whether or not this represents a p neoplastic change.

The recommended frequency and duration of administrat should not be exceeded (see Dosage and Administration).

Precautions. The diagnosis of keratoconjunctivitis due to Herp simplex virus should be established clinically prior to prescrib Vira-A Ophthalmic Ointment, 3%.

Patients should be forewarned that Vira-A Ophthalmic Oi ment, 3%, like any ophthalmic ointment, may produce a tempor visual haze.

Although viral resistance to Vira-A has not been observed, t possibility may exist.

Adverse Reactions. Lacrimation, foreign-body sensation, c junctival injection, burning, irritation, superficial punct keratitis, pain, photophobia, punctal occlusion, and sensiti have been reported with Vira-A Ophthalmic Ointment, 3%. T following have also been reported but appear disease-relat uveitis, stromal edema, secondary glaucoma, trophic defects, c neal vascularization, and hyphema.

Overdosage. Acute massive overdosage by oral ingestion of ophthalmic ointment has not occurred. However, the ra deamination to arabinosylhypoxanthine should preclude a difficulty. The oral LD_{50} for vidarabine is greater than 5,020 n kg in mice and rats. No untoward effects should result from ing tion of the entire contents of a tube.

Overdosage by ocular instillation is unlikely because any cess should be quickly expelled from the conjunctival sac. frequent administration should be avoided.

Dosage and Administration. Administer approximately one h inch of Vira-A Ophthalmic Ointment, 3%, into the lower c junctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or compl re-epithelialization has not occurred by 21 days, other forms therapy should be considered. Some severe cases may requ longer treatment.

After re-epithelialization has occurred, treatment for an ad tional seven days at a reduced dosage (such as twice daily) recommended in order to prevent recurrence.

How Supplied. N 0071-3677-07 (Stock 18-1677-139)

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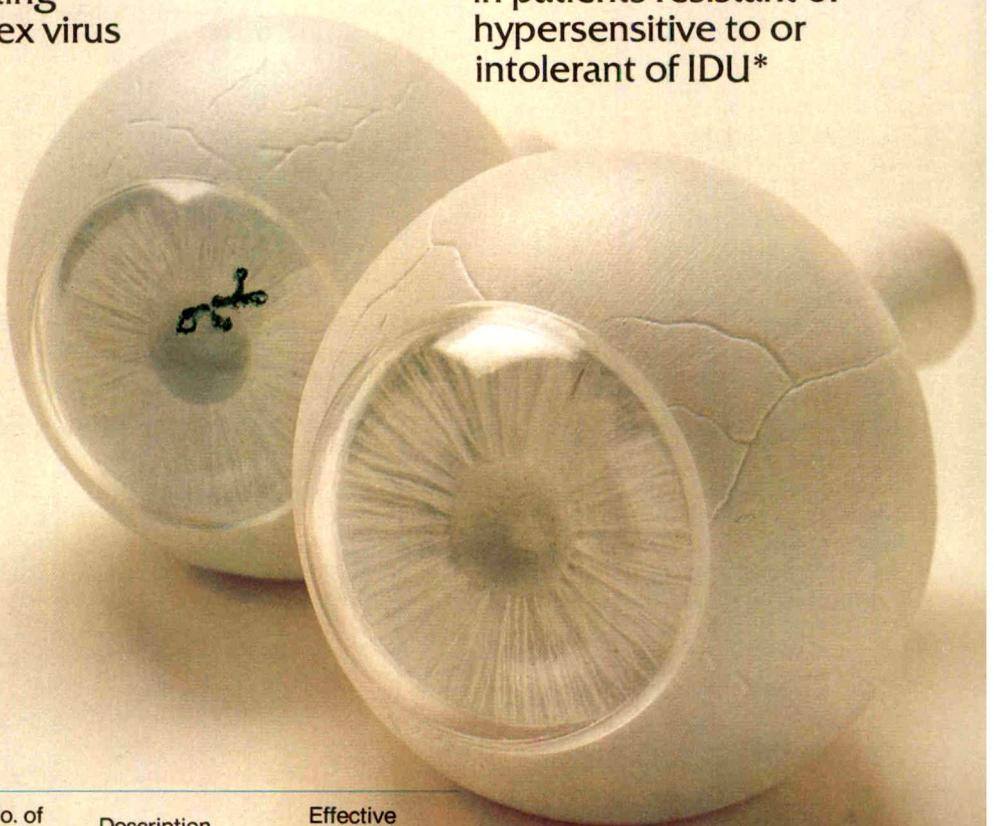

ical Evidence	No. of Subjects	Description	Effective Response
-A trolled Trials	81	Previously untreated	70 subjects **(86%)**
-A ontrolled Trials	142	75% had been resistant or hypersensitive to IDU	101 subjects **(71%)**

TE: In the controlled and uncontrolled trials, 70 and 101 subjects, ectively, re-epithelialized at the end of three weeks on Vira-A.

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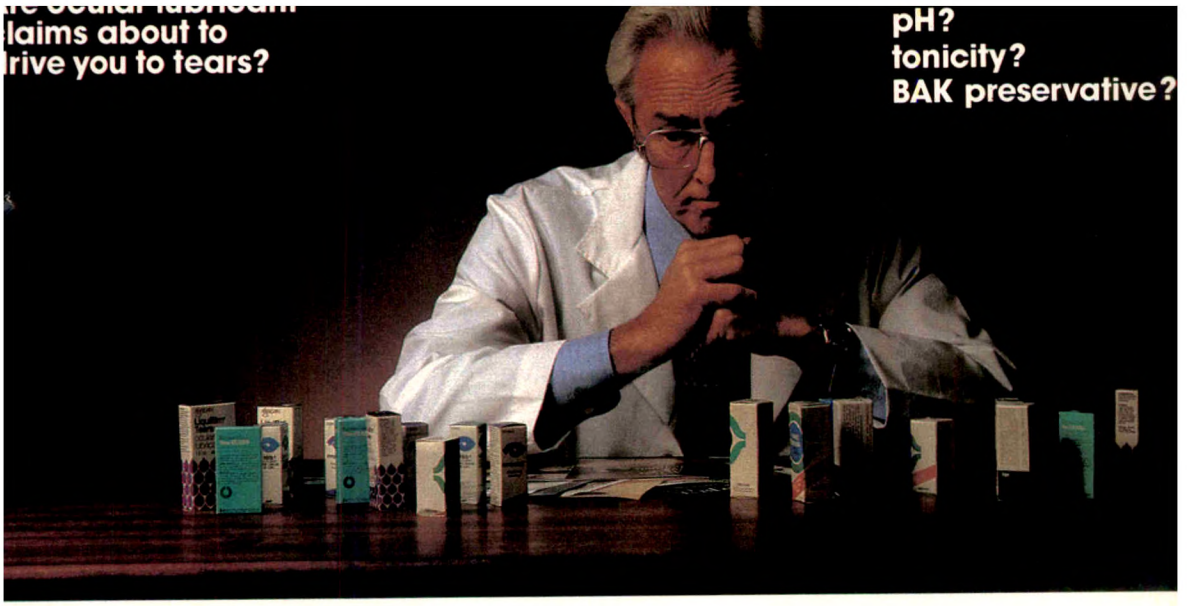

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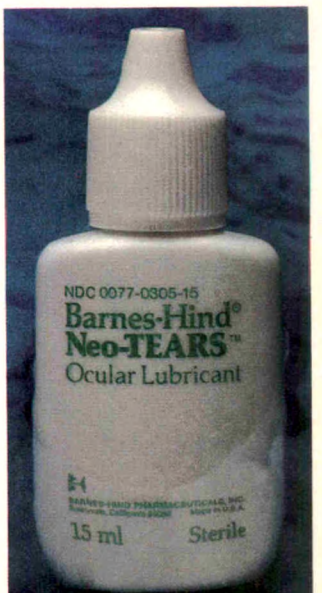

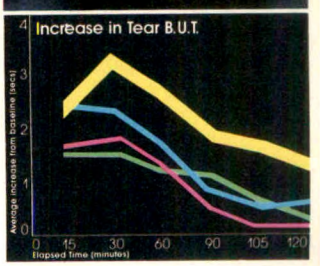

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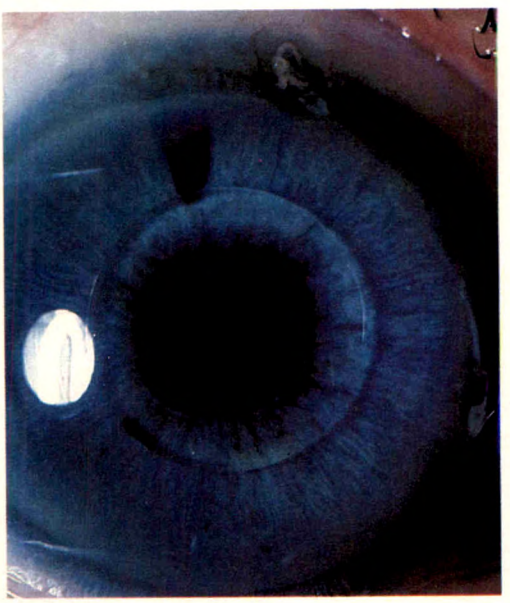

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1. Nelson, EL. Ophthalmic Steroids in Ocular Anti-Inflammatory Therapy. HE Kaufman, Editor, Springfield, ILL. Thomas, 1970.
2. Hull, FW and Epstein, WA. Comparison of the intraocular pressure effects of topical dexamethasone and fluorometholone. Allergan Report Series No. 74, 1972.

INDICATIONS — For steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. CONTRAINDICATIONS — Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. WARNINGS — Steroid medication in the treatment of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by presence of steroid medication. Safety and effectiveness have not been demonstrated in children of the age group 2 years or below. *Use in Pregnancy:* Safety of the use of topical steroids during pregnancy has not been established. PRECAUTIONS — As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intraocular pressure should be checked frequently. ADVERSE REACTIONS — Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe.

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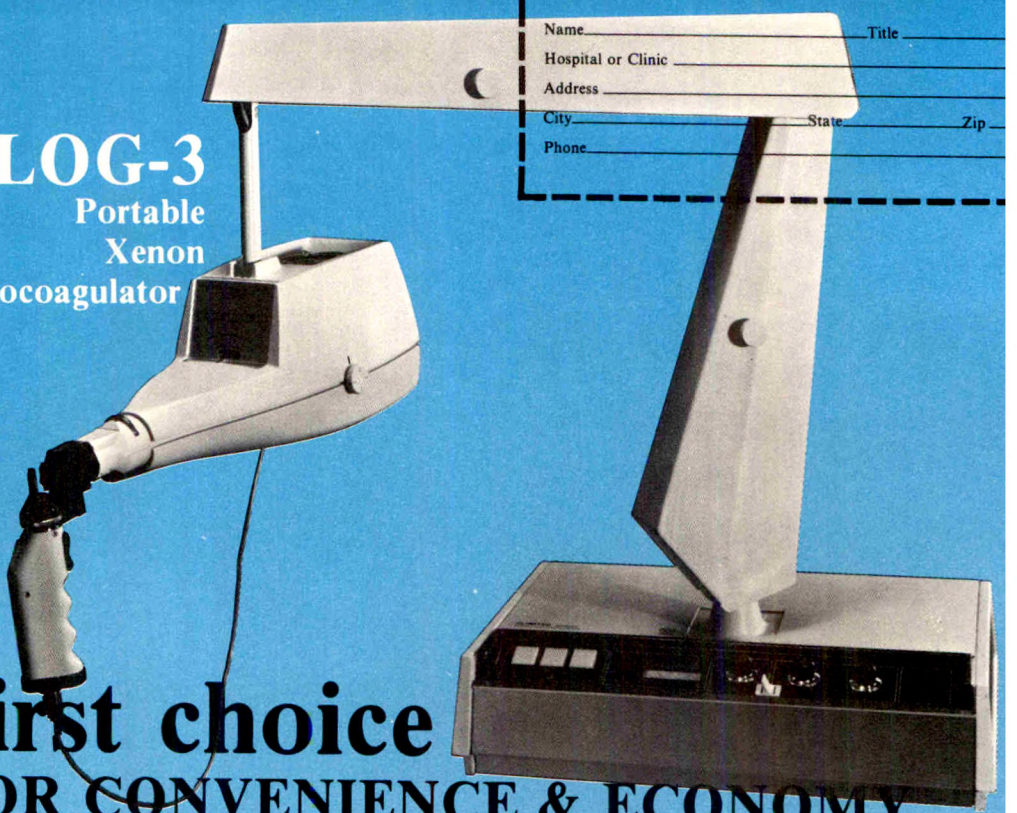

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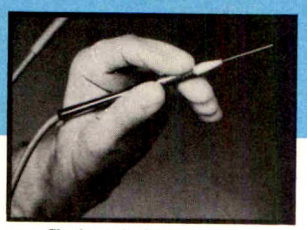

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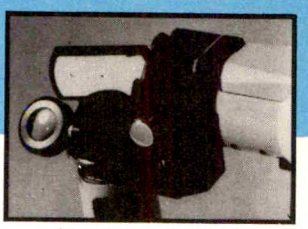

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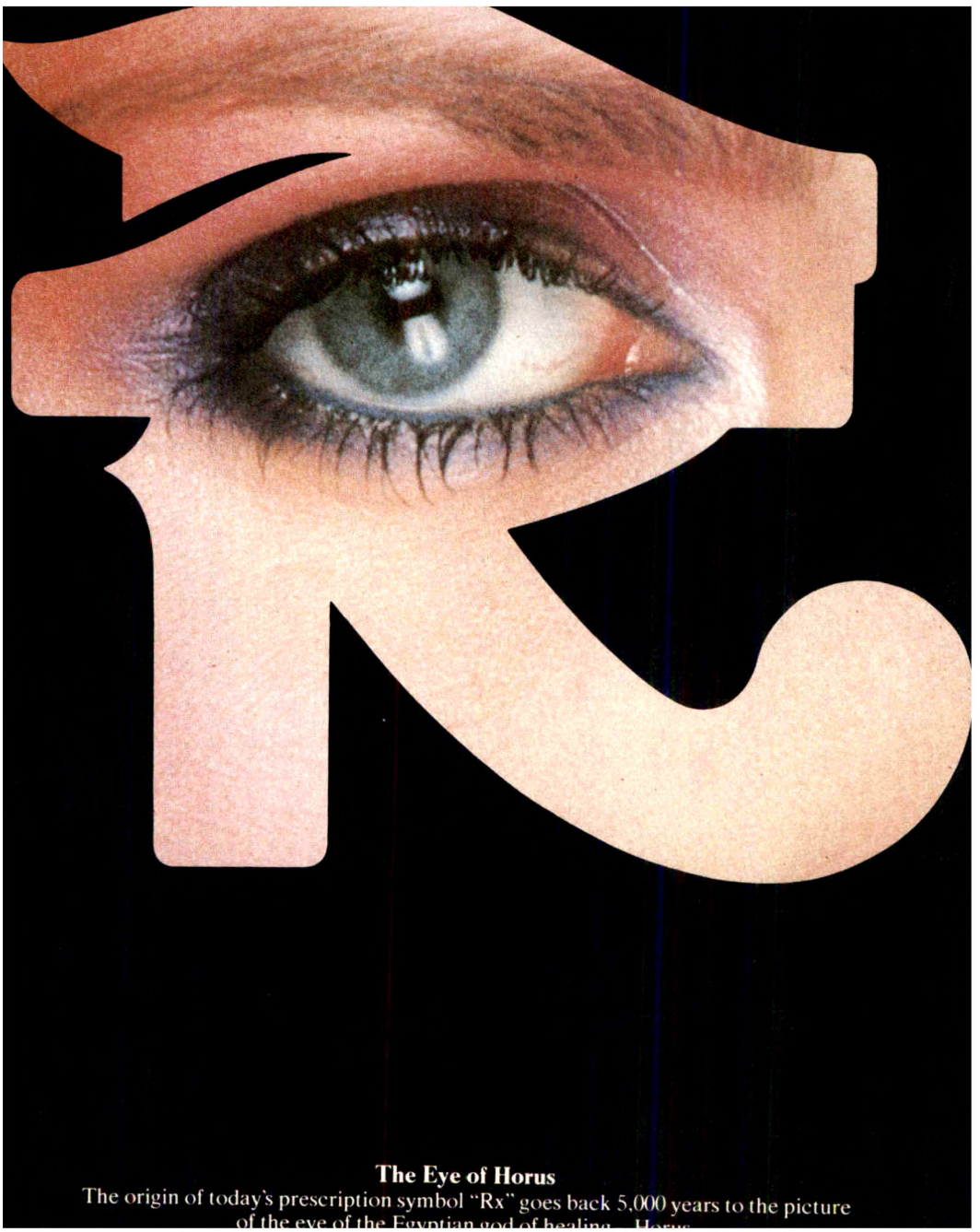

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For Topical Treatment of
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(Trifluridine)

OPHTHALMIC SOLUTION, 1%

STERILE

95% of Patients Responded

During controlled clinical trials 95% of patients (92 of 97) responded to VIROPTIC therapy. Dendritic and geographic ulcers were re-epithelialized in a mean time of 6 and 7 days, respectively.

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5 to 9 Drops Daily

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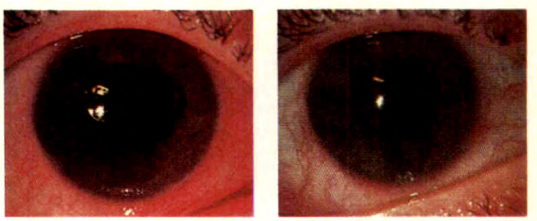

0 days 5 days after VIROPTIC therapy

Effective in 138 of 150 patients Unresponsive or Intolerant to Idoxuridine or Vidarabine

In studies of patients unresponsive or intolerant to idoxuridine or vidarabine, VIROPTIC demonstrated 92% effectiveness. Dendritic and geographic ulcers were re-epithelialized in a mean time of 6 and 12 days, respectively.

Please see following page for brief summary of prescribing information.

The First Antiviral Product From ONE HUNDRED YEARS WELLCOME **Burroughs Wellcome Co. Research**

VIROPTIC®
(Trifluridine)
OPHTHALMIC SOLUTION, 1%
STERILE

DESCRIPTION: VIROPTIC® is the brand name for trifluridine (also known as trifluorothymidine, F_3TdR,F_3T), an antiviral drug for topical treatment of epithelial keratitis caused by Herpes simplex virus. The chemical name of trifluridine is 5-trifluoromethyl-2′-deoxyuridine.

VIROPTIC sterile ophthalmic solution contains 1% trifluridine in an aqueous solution with acetic acid and sodium acetate (buffers), sodium chloride, and thimerosal 0.001% (added as a preservative).

CLINICAL PHARMACOLOGY: Trifluridine is a fluorinated pyrimidine nucleoside with *in vitro* and *in vivo* activity against Herpes simplex virus, types 1 and 2 and vacciniavirus. Some strains of Adenovirus are also inhibited *in vitro.*

Intraocular penetration of trifluridine occurs after topical instillation of VIROPTIC into human eyes. Decreased corneal integrity or stromal or uveal inflammation may enhance the penetration of trifluridine into the aqueous humor. Unlike the results of ocular penetration of trifluridine *in vitro,* 5-carboxy-2′-deoxyuridine was not found in detectable concentrations within the aqueous humor of the human eye.

INDICATIONS AND USAGE: VIROPTIC brand Trifluridine Ophthalmic Solution, 1% is indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus, types 1 and 2. VIROPTIC is also effective in the treatment of epithelial keratitis that has not responded clinically to the topical administration of idoxuridine or when ocular toxicity or hypersensitivity to idoxuridine has occurred. In a smaller number of patients found to be resistant to topical vidarabine, VIROPTIC was also effective.

The clinical efficacy of VIROPTIC in the treatment of stromal keratitis and uveitis due to Herpes simplex or ophthalmic infections caused by vacciniavirus and Adenovirus has not been established by well-controlled clinical trials. VIROPTIC has not been shown to be effective in the prophylaxis of Herpes simplex virus keratoconjunctivitis and epithelial keratitis by well-controlled clinical trials. VIROPTIC is not effective against bacterial, fungal or chlamydial infections of the cornea or nonviral trophic lesions.

During controlled multicenter clinical trials, 92 of 97 (95%) patients (78 of 81 with dendritic and 14 of 16 with geographic ulcers) responded to VIROPTIC therapy as evidenced by complete corneal re-epithelialization within the 14 day therapy period. In these controlled studies, 56 of 75 (75%) patients (49 of 58 with dendritic and 7 of 17 with geographic ulcers) responded to idoxuridine therapy. The mean time to corneal re-epithelialization for dendritic ulcers (6 days) and geographic ulcers (7 days) was similar for both therapies. In other clinical studies, VIROPTIC was evaluated in the treatment of Herpes simplex virus keratitis in patients who were unresponsive or intolerant to the topical administration of idoxuridine or vidarabine. VIROPTIC was effective in 138 of 150 (92%) patients (109 of 114 with dendritic and 29 of 36 with geographic ulcers) as evidenced by corneal re-epithelialization. The mean time to corneal re-epithelialization was 6 days for patients with dendritic ulcers and 12 days for patients with geographic ulcers.

CONTRAINDICATIONS: VIROPTIC brand Trifluridine Ophthalmic Solution, 1%, is contraindicated for patients who develop hypersensitivity reactions or chemical intolerance to trifluridine.

WARNINGS: The recommended dosage and frequency of administration should not be exceeded (see Dosage and Administration).

PRECAUTIONS:

General: VIROPTIC brand Trifluridine Ophthalmic Solution, 1% should be prescribed only for patients who have a clinical diagnosis of herpetic keratitis.

VIROPTIC may cause mild local irritation of the conjunctiva and cornea when instilled but these effects are usually transient.

Although documented *in vitro* viral resistance to trifluridine has not been reported following multiple exposure to VIROPTIC, the possibility exists of viral resistance development.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Mutagenic Potential. Trifluridine has been shown to exert mutagenic, DNA damaging and cell transforming activities in various standard *in vitro* test systems, and clastogenic activity in *Vicia faba* cells.

Although the significance of these test results is not clear or fully understood, there exists the possibility that mutagenic agents may cause genetic damage in humans.

Oncogenic Potential. The oncogenic potential of trifluridine is unknown at this time. The oncogenic potential of trifluridine in rodents is being evaluated.

Pregnancy: The drug should not be prescribed for pregnant women unless the potential benefits outweigh the potential risks.

Nursing Mothers: It is unlikely that trifluridine is excreted in human milk after ophthalmic instillation of VIROPTIC because of the relatively small dosage (≤5.0 mg/day), its dilution in body fluids and its extremely short half-life (approximately 12 minutes). The drug should not be prescribed for nursing mothers unless the potential benefits outweigh the potential risks.

ADVERSE REACTIONS: The most frequent adverse reactions reported during controlled clinical trials were mild, transient burning or stinging upon instillation (4.6%) and palpebral edema (2.8%). Other adverse reactions in decreasing order of reported frequency were superficial punctate keratopathy, epithelial keratopathy, hypersensitivity reaction, stromal edema, irritation, keratitis sicca, hyperemia, and increased intraocular pressure.

OVERDOSAGE: Overdosage by ocular instillation is unlikely because any excess solution should be quickly expelled from the conjunctival sac.

Acute overdosage by accidental oral ingestion of VIROPTIC has not occurred. However, should such ingestion occur, the 75 mg dosage of trifluridine in a 7.5 ml bottle of VIROPTIC is not likely to produce adverse effects. Single intravenous doses of 15-30 mg/kg/day in children and adults with neoplastic disease produce reversible bone marrow depression as the only potentially serious toxic effect and only after 3-5 courses of therapy. The acute oral LD_{50} in the mouse and rat was 4379 mg/kg or higher.

DOSAGE AND ADMINISTRATION: Instill one drop of VIROPTIC Ophthalmic Solution, 1% onto the cornea of the affected eye every two hours while awake for a maximum daily dosage of nine drops until the corneal ulcer has completely re-epithelialized. Following re-epithelialization, treatment for an additional seven days of one drop every four hours while awake for a minimum daily dosage of five drops is recommended.

If there are no signs of improvement after seven days of therapy or complete re-epithelialization has not occurred after 14 days of therapy, other forms of therapy should be considered. Continuous adminsitration of VIROPTIC for periods exceeding 21 days should be avoided because of potential ocular toxicity.

HOW SUPPLIED: VIROPTIC Ophthalmic Solution, 1% is supplied as a sterile ophthalmic solution in a plastic Drop-Dose® dispenser bottle of 7.5 ml.

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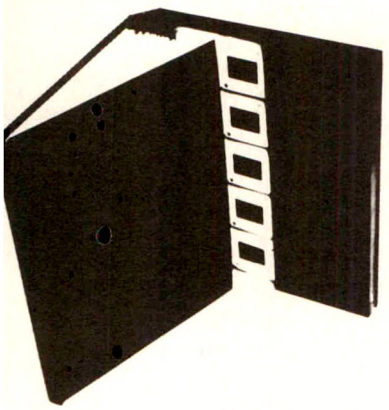

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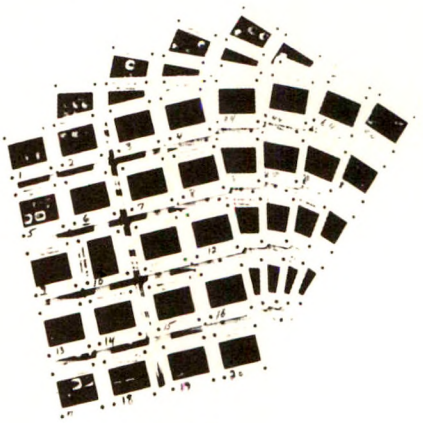

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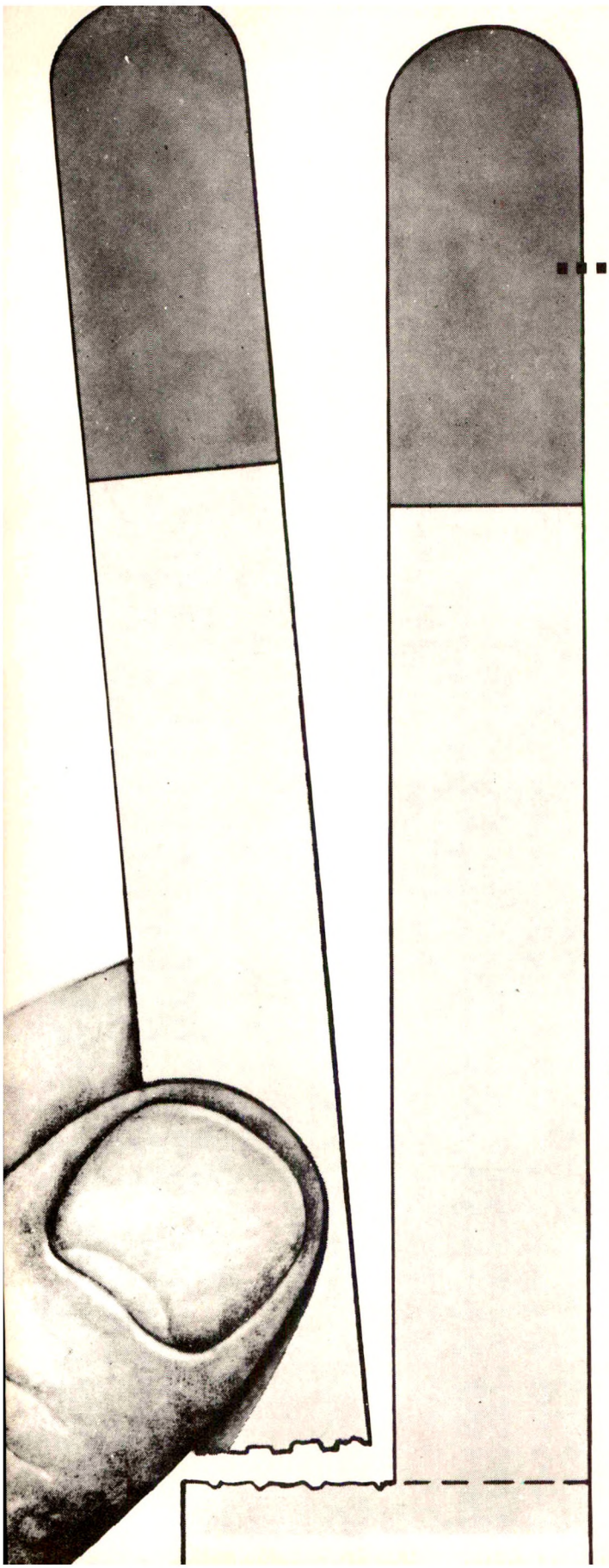

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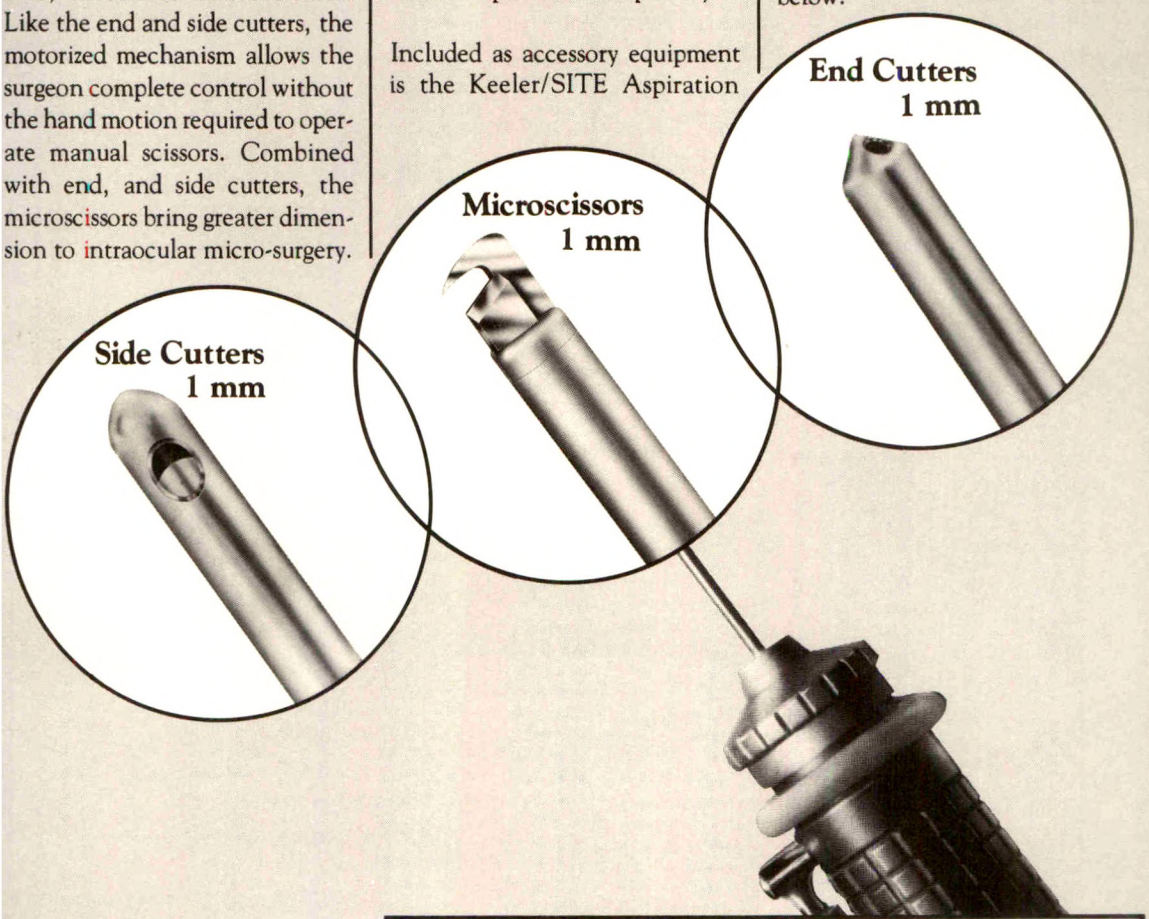

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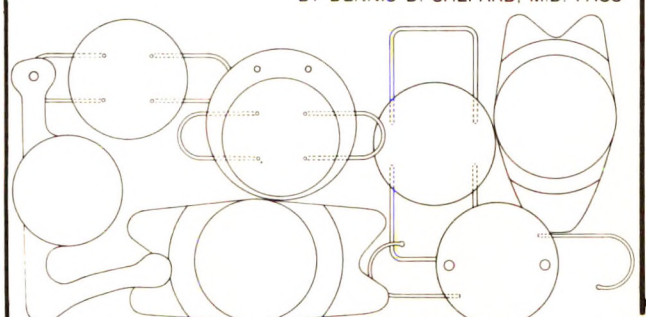

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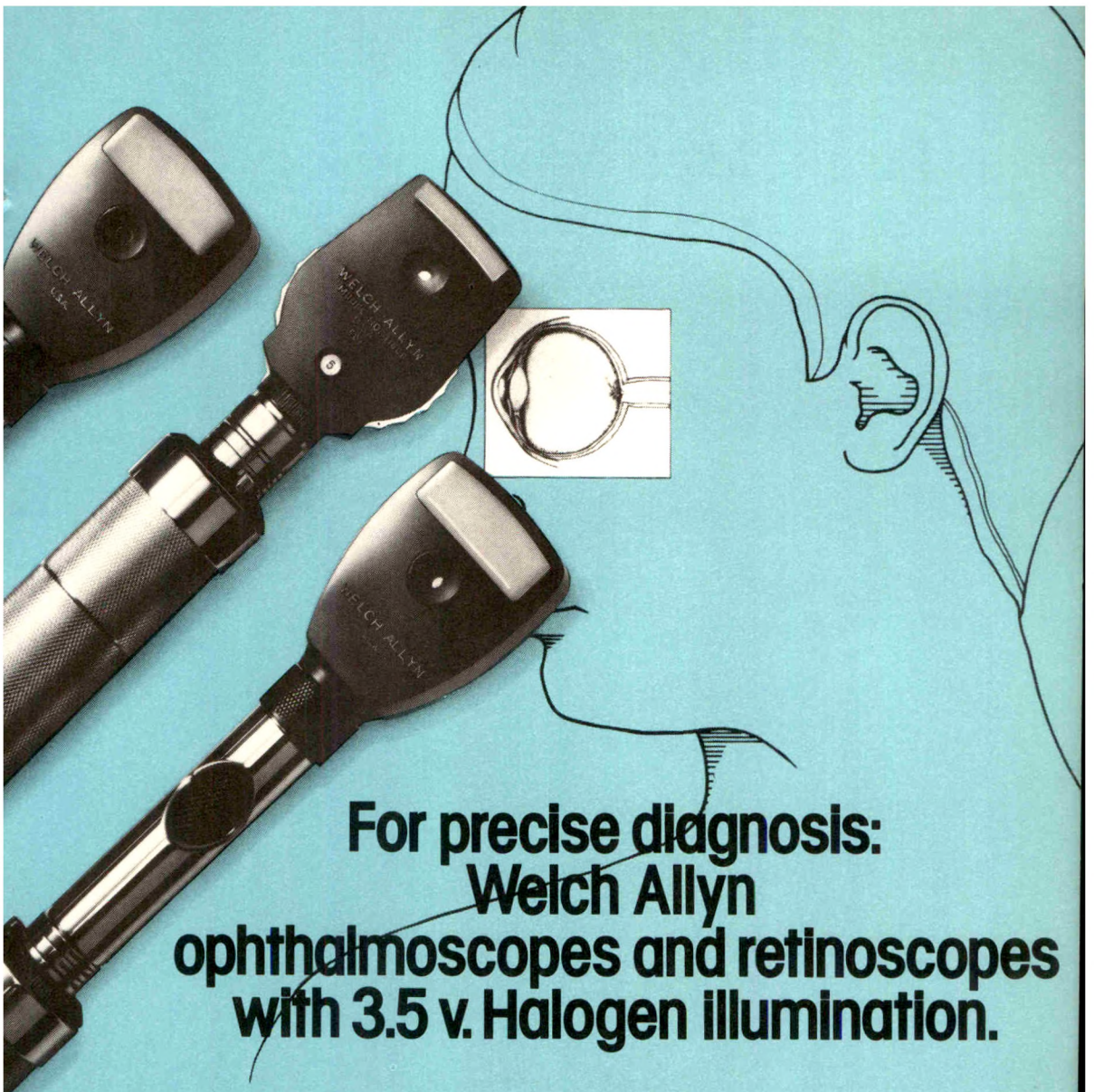

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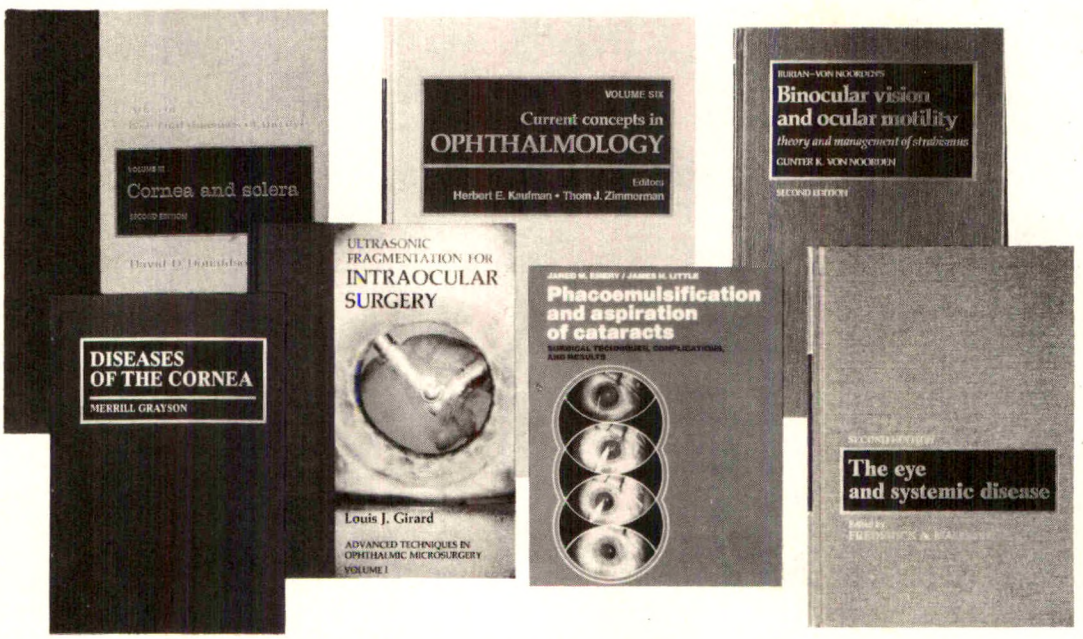

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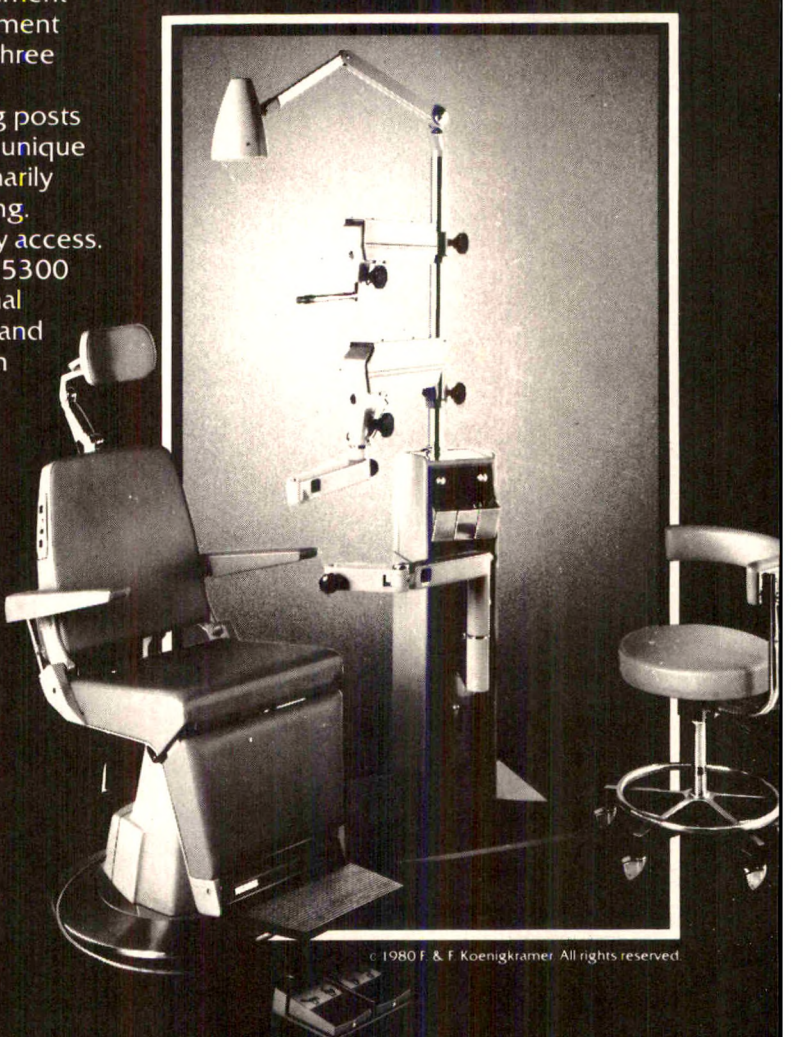

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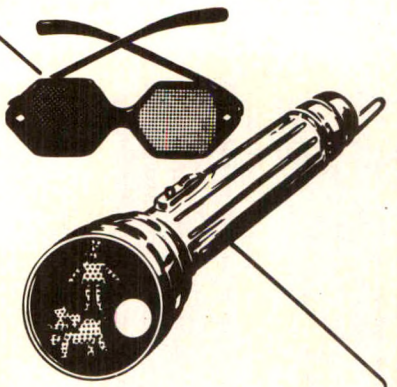

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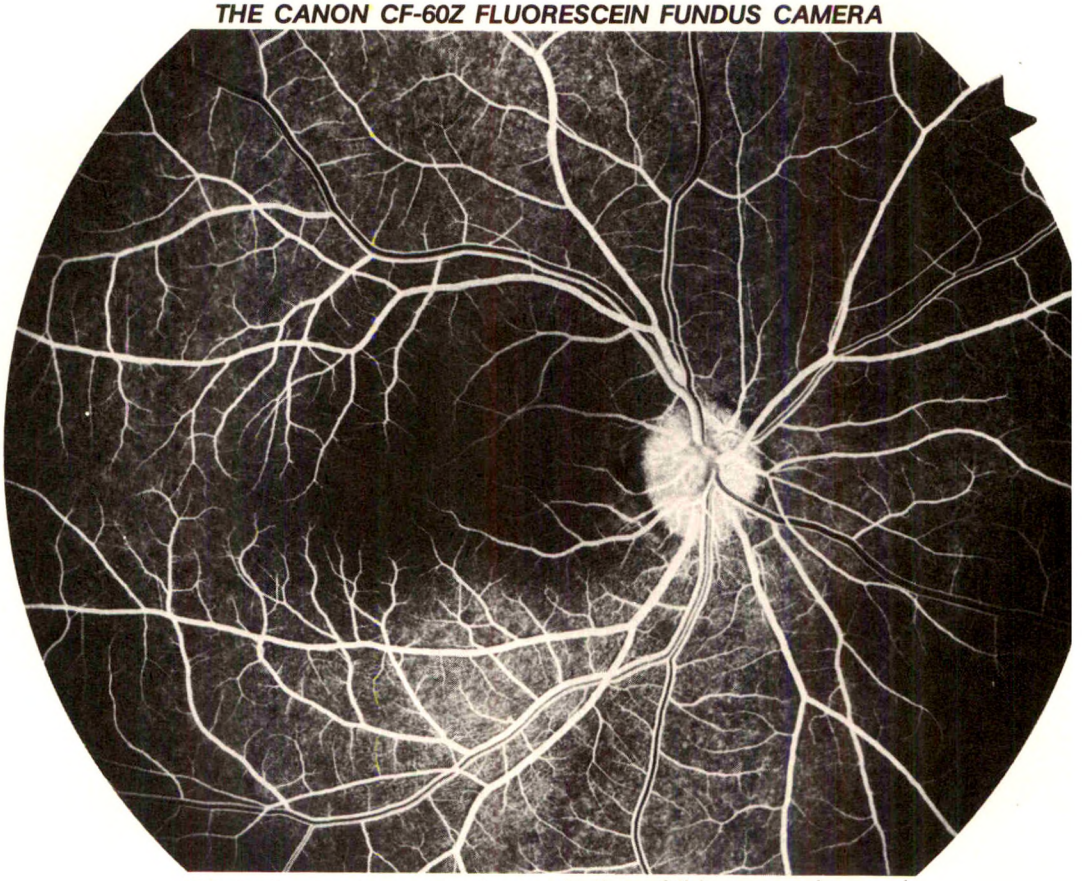

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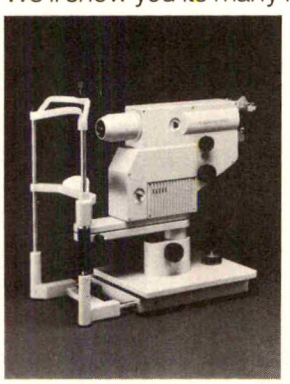

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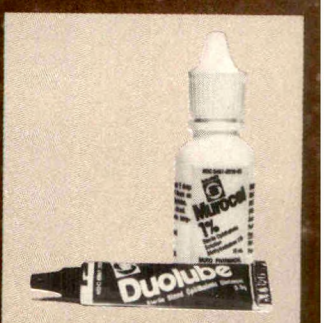

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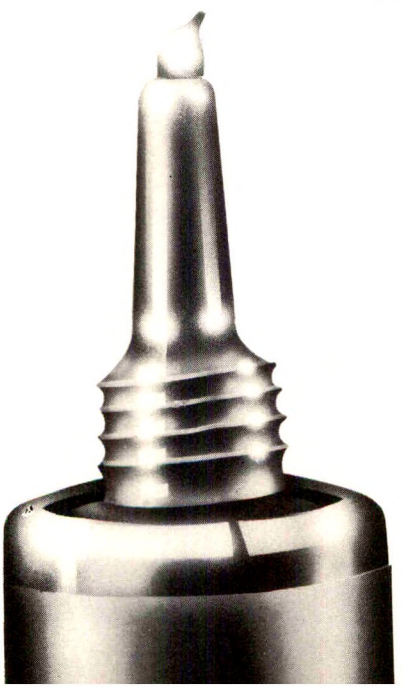

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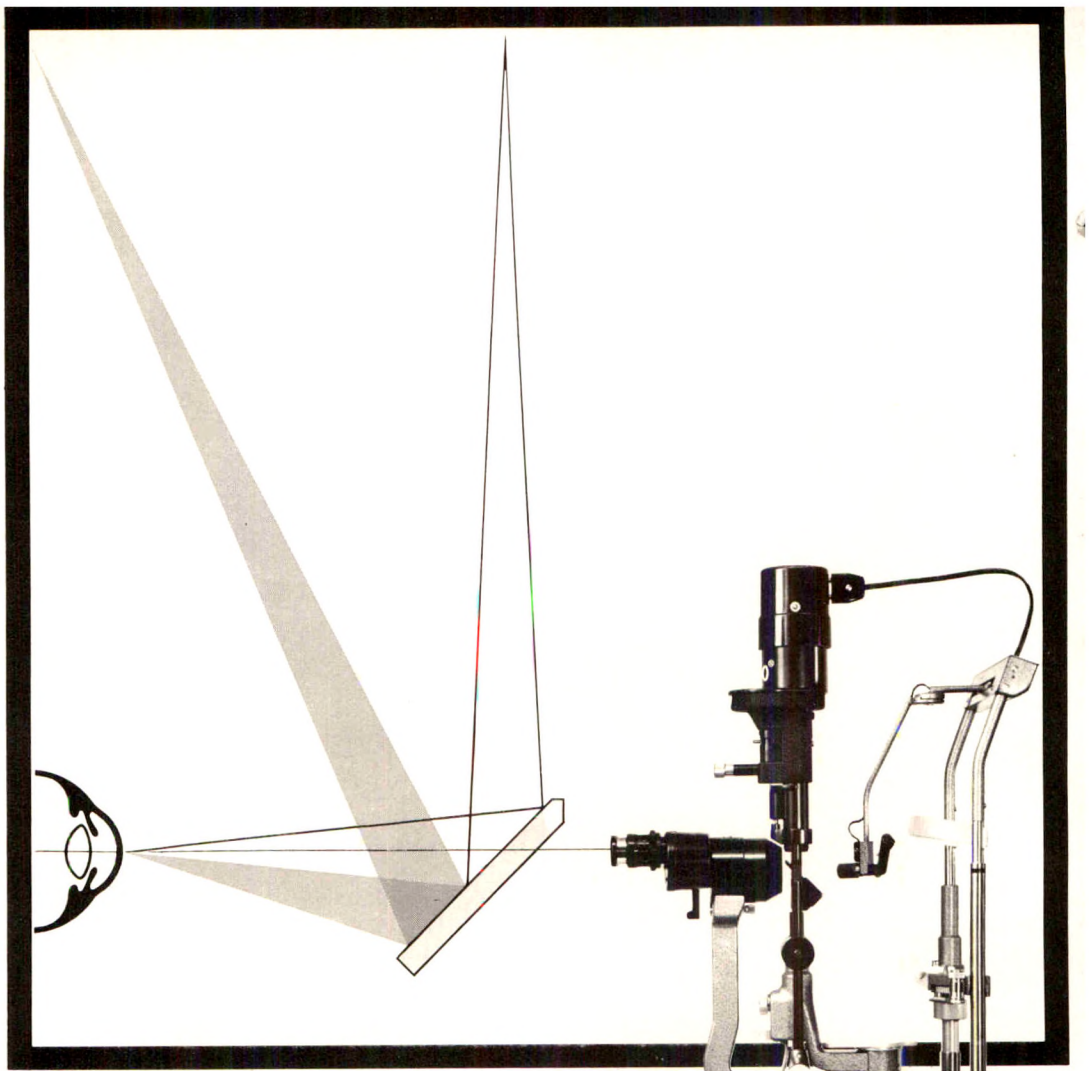

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When it comes to providing the best possible patient care, the real thing is needed, the best possible Slit Lamp... the SL-900® by Haag-Streit. To experience optical resolution as it really should be... to observe details with the truly finest slit system... and to arrive at an unquestionably assured diagnosis, rely on the original. The finest skills can only be excercised with the finest instruments. Such instruments cost more because they do more. Over 10,000 U.S. Haag-Streit SL-900® users know what this means. If you don't, move up now to the original. Contact us for full details on the SL-900® and a free copy of Haag-Streit's book, «On Slit Lamp Microscopy», or get in touch with your local Haag-Streit distributor.

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Subsidiary of Haag-Streit AG., Berne, Switzerland
6 Industrial Park, Waldwick, New Jersey 07463
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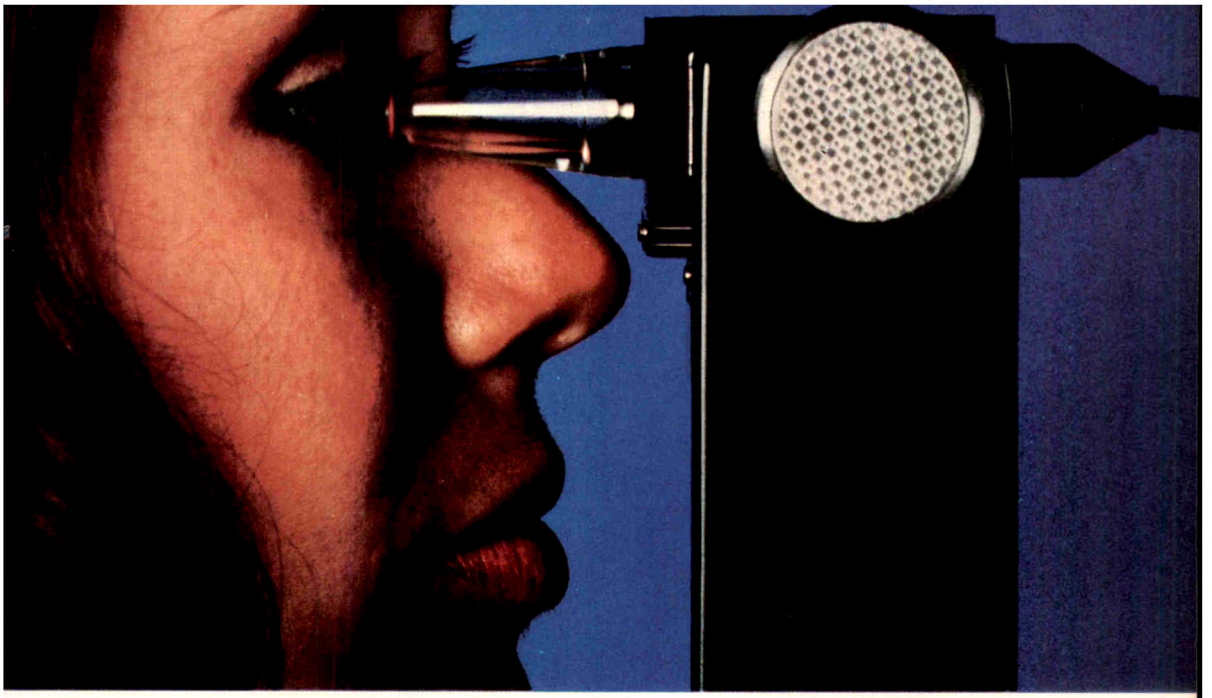

Measurements, not estimates of IOL power

The DBR-300 brings extreme precision to intraocular ens power determinations. Accuracy to within a quarter of diopter has been proven in clinical use for over 4 years. nd maximum performance is maintained even in cases of ense, mature cataracts.

Axial length measurements are digitally displayed along ith the A-scan trace, and the probe mounting design inimizes globe distortion and patient discomfort. The esult: rapid, simple examinations conducted in minutes, asy documentation, and maximum performance. The igital Biometric Ruler Model DBR-300 is as easy to oper- te as an applanation tonometer. Full A-mode diagnostic apabilities also permit detection and diagnosis of ocular nd orbital pathology.

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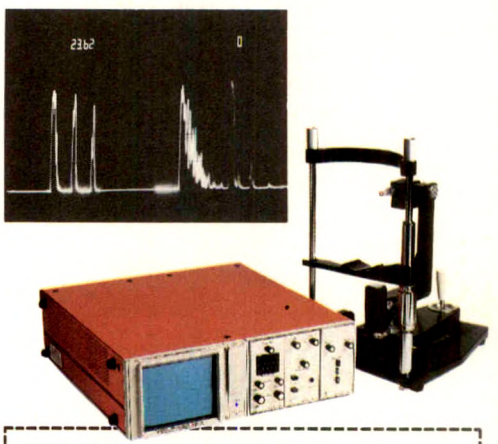
Accurate. Reliable. Clincally proven. The DBR-300 ives you the data needed to minimize dioptric errors. onometrics also provides the most advanced system for OL calculations: the Binkhorst module for easy use in the exas Instruments TI-58/59 printing calculators.

And the DBR-300 is fully backed by the technical ervices and assistance of Sonometrics, the first and ost advanced company in ophthalmic ultrasound. Call ll-free (800) 223-0412 or mail the coupon at right for dditional details.



DBR-300/Sonometrics Systems, Inc.
16 West 61st Street, New York, New York 10023
AJO-5

Name_____
Affiliation_____
Address_____
City_____ State_____ Zip_____
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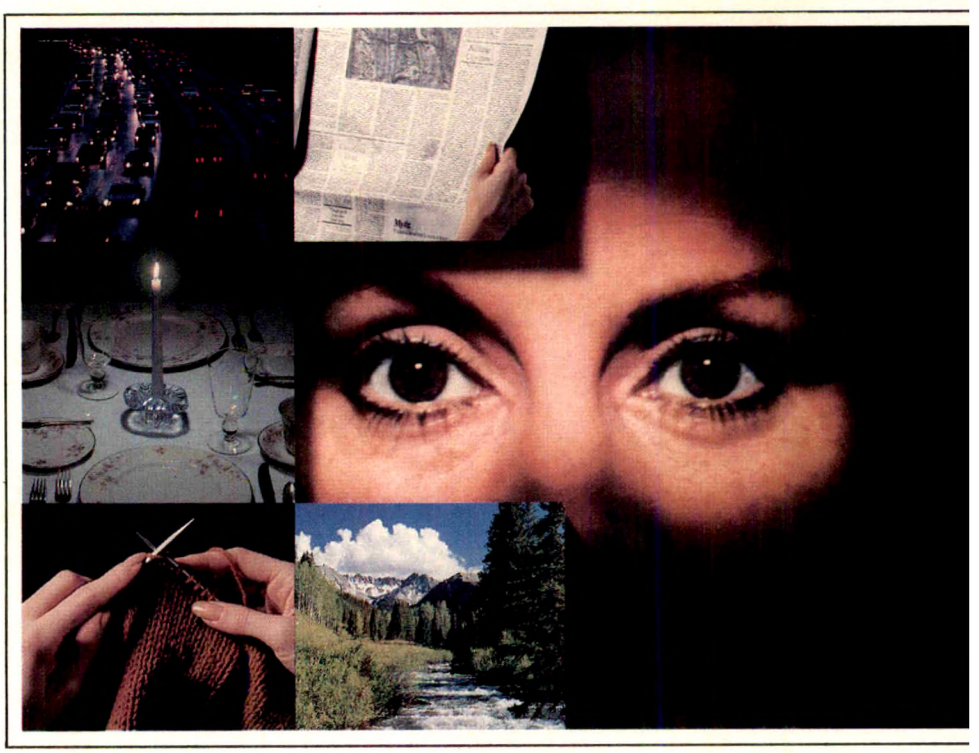
DBR-300
DIGITAL BIOMETRIC RULER
SONOMETRICS SYSTEMS, INC

A Rorer Group Company

In chronic open-angle glaucoma therapy

Two good reasons to switch patients to



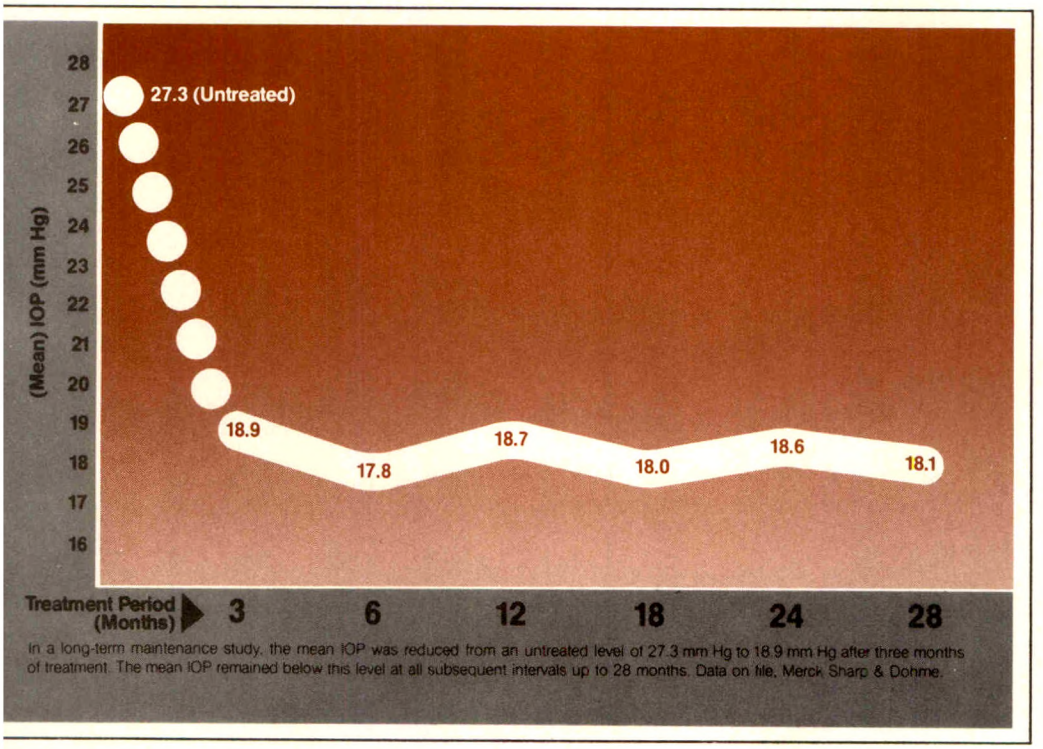
1. A better quality of life for many patients...

Patients on TIMOPTIC® (Timolol Maleate, MSD) generally do *not* experience the following therapy-limiting side effects:

change in pupil size/dimming of vision/night blindness*

TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product. Occasionally, mild ocular irritation has been reported.

Timoptic®
(TIMOLOL MALEATE | MSD)
OPHTHALMIC SOLUTION



In a long-term maintenance study, the mean IOP was reduced from an untreated level of 27.3 mm Hg to 18.9 mm Hg after three months of treatment. The mean IOP remained below this level at all subsequent intervals up to 28 months. Data on file, Merck Sharp & Dohme.

2. Efficacy maintained in long-term therapy...

- No tolerance was observed in 102 patients for 28 months
- TIMOPTIC was significantly more effective than pilocarpine or epinephrine in reducing elevated IOP*
- TIMOPTIC reduced IOP in 3 out of 4 patients*

*Based on controlled multiclinic studies, evaluating over 1000 patients.

MSD MERCK SHARP DOHME

For a brief summary of Prescribing Information, please see following page. Copyright © 1979 by Merck & Co., Inc.

NOW AVAILABLE
NEW
10-ml OCUMETER®

Timoptic®
(TIMOLOL MALEATE | MSD) OPHTHALMIC SOLUTION

a beta-adrenergic blocking agent in ophthalmic solution

a significant advance for the reduction of IOP in:

- chronic open-angle glaucoma
- aphakic glaucoma
- some patients with secondary glaucoma
- patients with elevated intraocular pressure at sufficient risk to require lowering of the ocular pressure
- some patients who respond inadequately to multiple antiglaucoma drug therapy

How to start patients on TIMOPTIC:
Usual starting dosage: one drop 0.25% TIMOPTIC in each eye twice a day.

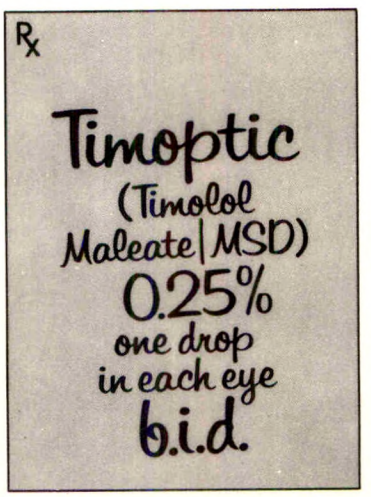
How to transfer from current therapy to TIMOPTIC:
1. On the first day: continue with the agent(s) already being used and add one drop 0.25% TIMOPTIC in each eye b.i.d.

2. On the second day: discontinue the previously used agent(s) and continue with TIMOPTIC in each eye b.i.d.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in each eye. Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in each eye.

Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

In patients with a history of severe cardiac disease, pulse rates should be checked.



CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients who are hypersensitive to any component of this product.
PRECAUTIONS: Should be used with caution in patients with known contraindications to systemic use of beta-adrenergic receptor blocking agents. These include bronchial asthma; sinus bradycardia and greater than first-degree block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; concomitant use with adrenergic-augmenting psychotropic drugs. In patients with a history of severe cardiac disease, pulse rates should be checked. Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Sufficient clinical data have not been obtained to show safety or efficacy in narrow-angle or angle-closure glaucoma.
Pregnancy: TIMOPTIC has not been studied in human pregnancy. The use of TIMOPTIC in pregnant women requires that the anticipated benefit be weighed against possible hazards.
Use in Children: Since clinical studies in children have not been done, TIMOPTIC is not recommended for use in children at this time.
ADVERSE REACTIONS: In clinical trials of up to three years duration prior to release in 1978, signs and symptoms of mild ocular irritation were reported occasionally. Local hypersensitivity reactions, including localized and generalized rash, have occurred rarely.

Slight reduction of the resting heart rate (mean reduction 2.9 beats/minute, standard deviation 10.2) has been observed in some patients. Rarely, episodes of acute bronchospasm have been reported in patients with bronchospastic disease (see PRECAUTIONS).
Note: TIMOPTIC has been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. TIMOPTIC has not been studied in patients wearing lenses made with materials other than PMMA.
HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 5-ml and 10-ml plastic OCUMETER® Ophthalmic Dispensers with a controlled drop tip.
580 (DC7046009)

MSD
MERCK SHARP & DOHME

For more detailed information, consult your MSD representative and the full Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

A THIN, HIGHER WATER CONTENT SOFT LENS MEANS GREATER PATIENT ACCEPTANCE FOR YOU.

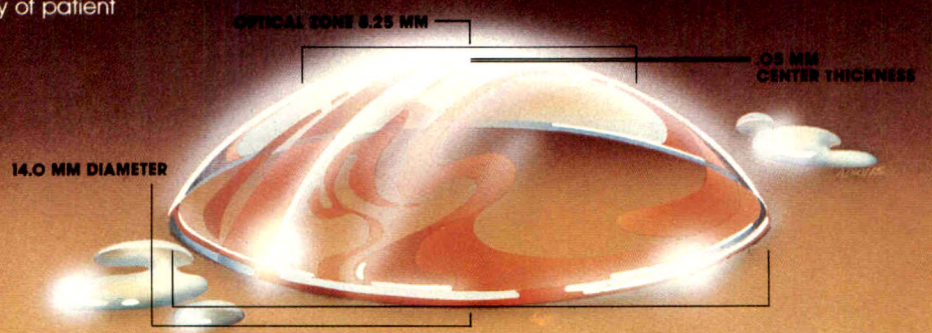
The two most important properties of a contact lens have now been integrated into one lens design—the thin, 55% water content HYDROCURVE II-55 Contact Lens. This new, synergistic concept of a thin, high-water content lens combines the practicality of increased oxygen transmissibility with the reality of patient comfort.

Greatest oxygen transmissibility. With a center thickness of only .05 mm, the new 55% water content HYDROCURVE II Contact Lens transmits more oxygen than any other daily wear soft contact lens. The average thickness of a -3.00 D lens across the optical zone is only .08 mm, so that even at its thickest point the lens facilitates oxygen transport.

Engineered for fitting ease. The 14.0 mm diameter 8.5 mm base curve lens provides excellent centration for practically all corneal sizes and topographies. Only a small trial set is needed for diagnostic efficiency and a small fitting set will give you SAME DAY dispensing capability for most myopes.

Compatible with corneal metabolism. The 55% water content lens complements the natural corneal environment.

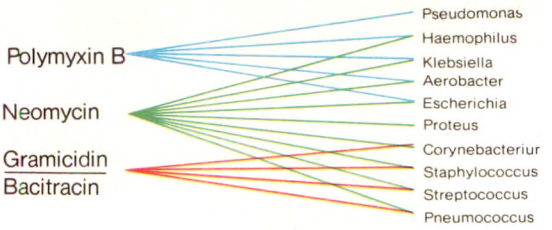
Ease of handling. The 14.0 mm diameter lends dimensional stability to the thin lens profile so lens handling is simplified. Chemical disinfection is recommended to prolong the useful life of the lens.



HYDROCURVE II is a registered trademark of Soft Lenses, Inc., San Diego, California.

HYDROCURVE SOFT LENSES, INC.
A SUBSIDIARY OF CONTINUOUS CURVE CONTACT LENSES, INC.
8006 ENGINEER ROAD, SAN DIEGO, CALIFORNIA 92111
(800) 854-2790. IN CALIFORNIA (800) 542-6000. (714) 277-9873

effectively cover the spectrum of superficial external ocular infections



with

NEOSPORIN®

Ophthalmic Solution Sterile
(Polymyxin B–Neomycin–Gramicidin)

when eyes need to be open and vision clear, eye drops may be the more appropriate choice

solution will not cause blurring

NEOSPORIN®

Ophthalmic Ointment Sterile
(Polymyxin B–Bacitracin–Neomycin)

when patient is sleeping, an ointment may be the more suitable selection for closed eyes

ointment base keeps antibacterials in prolonged contact with the eye

Burroughs Wellcome Co
Research Triangle Park
North Carolina 27709

See adjacent page for brief prescribing information

NEOSPORIN®
Ophthalmic Solution Sterile
(Polymyxin B–Neomycin–Gramicidin)

Each cc contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; neomycin sulfate 2.5 mg (equivalent to 1.75 mg neomycin base); gramicidin 0.025 mg. Vehicle contains alcohol 0.5%, thimerosal (preservative) 0.001% and the inactive ingredients propylene glycol, polyoxyethylene polyoxypropylene compound, sodium chloride and purified water.

NEOSPORIN®
Ophthalmic Ointment Sterile
(Polymyxin B–Bacitracin–Neomycin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 Units; zinc bacitracin 400 Units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.

Brief Disclosure below applies to the solution and ointment.

INDICATIONS: For the short-term treatment of superficial external ocular infections caused by organisms susceptible to one or more of the antibiotics contained therein.

CONTRAINDICATIONS: Contraindicated in those persons who have shown sensitivity to any of the components.

WARNINGS: Prolonged use may result in overgrowth of nonsusceptible organisms. Ophthalmic Ointment may retard corneal healing.

PRECAUTIONS: Culture and susceptibility testing should be performed during treatment.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Complete literature available on request from Professional Services Dept. PML.

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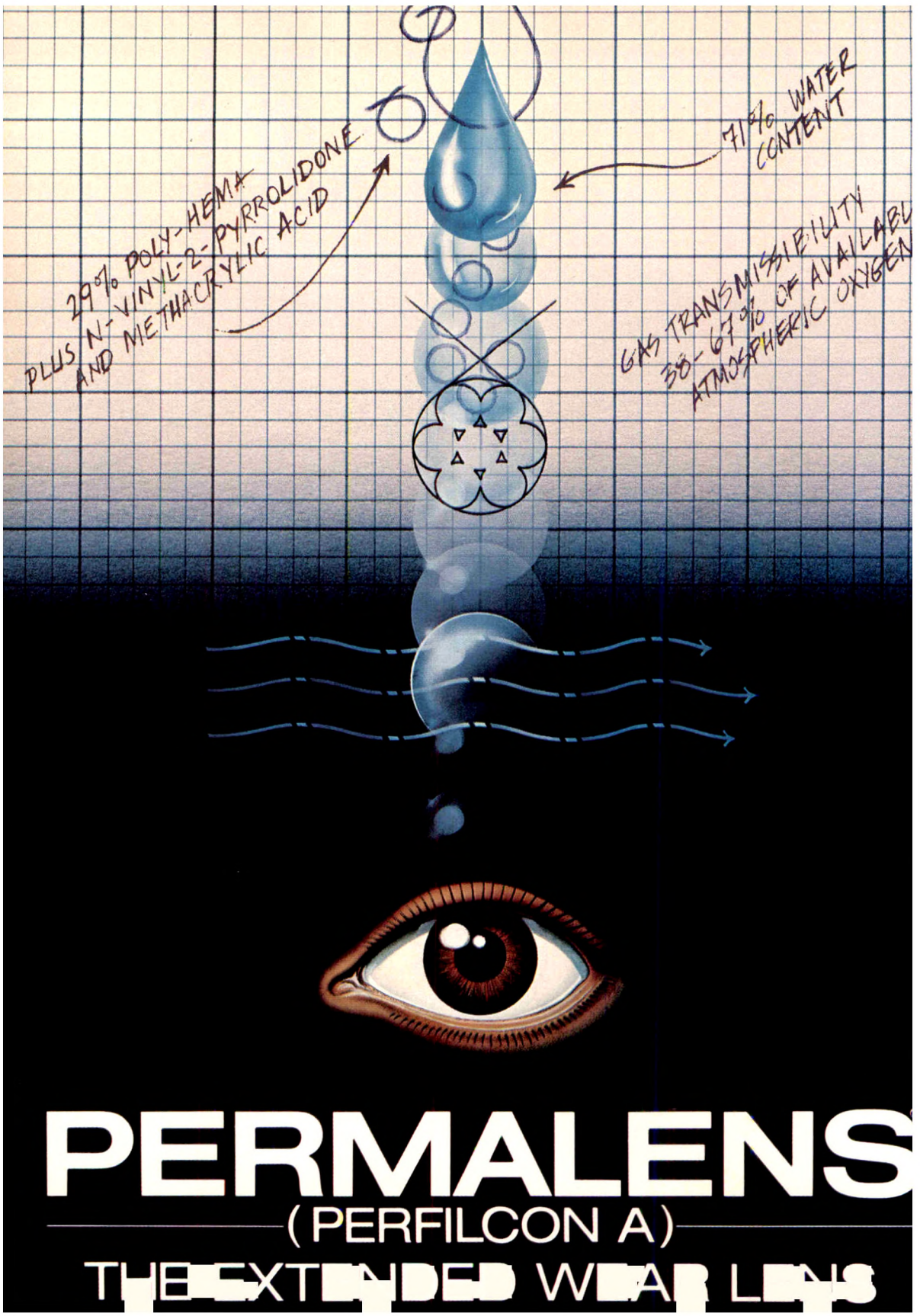

PERMALENS

(PERFILCON A)

THE EXTENDED WEAR LENS

Permalens® Contact Lenses: not just extended wear of a lens, but a lens **designed specifically for extended wear.**

That's why Permalens® Contact Lenses are rapidly changing the field of vision correction. Now your aphakic patients can again experience near-normal vision from the moment they wake up in the morning. Without the bother of daily insertion and removal.

And because of their advanced design, Permalens® Contact Lenses exhibit a physiological response comparable to daily-wear soft lenses. Even though your patients wear them 24 hours a day, for weeks at a time. The long-term acceptance of Permalens® Contact Lenses has been proven through extensive clinical trials.

This response is partly due to the Permalens® material, perfilcon A, which combines high water content, high oxygen permeability, and dimensional stability. These properties were designed into the lens to facilitate oxygen transfer directly through the lens, so the cornea can receive an oxygen supply adequate to maintain itself in a healthy state.

These properties also make Permalens® Contact Lenses more supple, and therefore comfortable on the patient's eyes. Patients have reported, in fact, they're the next best thing to wearing no lens at all.

Easy to fit, Permalens® Contact Lenses are available in a range of powers from +11.00 to +17.00 diopters. And with just four parameters, the lens fits most corneal sizes and curvatures.

Maintenance, too, is uncomplicated. Since Permalens® Contact Lenses usually need only be removed once a month, cleaning and disinfection are simplified. The preferred regimen is Preflex®/Flexsol®/Normol.® (Thermal regimens can also be used.) For re-hydration during lens wear, Clērz® or Adapettes® eye drops are available.

Patient comfort and convenience . . . clinically proven safety . . . easy fitting . . . simple maintenance. Good reasons why thousands of patients and practitioners alike have accepted Permalens® as the extended-wear lens.

Permalens®
(perfilcon A)

Hydrophilic Contact Lens
For Extended Wear
Post-Cataract (Aphakic) Use

For full prescribing information, see next page.

Now available nation-wide. For details, contact your representative or call:

Cooper

Cooper Laboratories, Inc.
Permalens Division
265 N. Whisman Road
Mountain View, California 94043
(800) 227-8170
In California: (415) 968-1630
or (800) 982-5832

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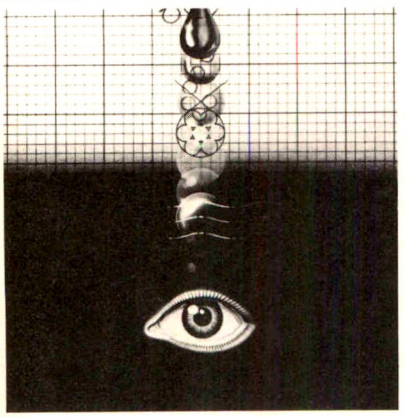

Permalens®
(perfilcon A)

Hydrophilic Contact Lens For Extended Wear Post-Cataract (Aphakic) Use

DESCRIPTION

The **Permalens®** (perfilcon A) Hydrophilic Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, perfilcon A, is a terpolymer of 2-hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone, and methacrylic acid, with ethyleneglycol dimethacrylate as a crosslinking agent. The hydrated lens consists of 29% perfilcon A and 71% water by weight. The gas permeability of **Permalens®** Hydrophilic Contact Lenses, using the Fatt method[1] has been determined to be: 42.0×10^{-11} $cm^2 \cdot ml\ O_2/sec \cdot ml \cdot mm\ Hg$ at 36°C.

ACTIONS

When placed on the human cornea, the hydrated **Permalens®** Hydrophilic Contact Lens acts as a refracting medium to compensate spherical ametropias.

INDICATIONS AND USAGE

Aphakia

Permalens® (perfilcon A) Hydrophilic Contact Lenses are indicated for extended-wear aphakic vision correction in persons with non-diseased eyes.

Note: Supplemental spectacles may be required, in some conditions, to provide near vision or to compensate for uncorrected refractive astigmatism.

CONTRAINDICATIONS

Permalens® Hydrophilic Contact Lenses are contraindicated by the presence of any of the following conditions:

1. Acute and subacute inflammations of the anterior segment of the eye.
2. Any eye disease which affects the cornea or conjunctiva.
3. Insufficiency of lacrimal secretion.
4. Corneal hypoesthesia.
5. Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS

Abrasions and Infections

If a lens becomes less comfortable than it was when it was first placed on the wearer's cornea, the lens should be removed and inspected for the presence of a foreign body, lens coating, deposits, or lens damage. If examination of the patient's eye reveals any eye abrasion, ulceration, irritation or infection, or any other abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Patients should not be fitted with Permalens® (perfilcon A) Hydrophilic Contact Lenses during the post-operative period until, in the opinion of the surgeon, the eye has healed completely.

Medications and Eye Drops

Permalens® Hydrophilic Contact Lenses must be stored in an appropriate solution when off the eyes. The solution used is dependent on the system selected for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored in PERMASOL™ Rinsing and Storage Solution (sterile buffered balanced salt solution preserved with edetate disodium 0.1% and thimerosal 0.001%) or BOILnSOAK® Sterile Saline Solution (sterile buffered isotonic solution containing boric acid, sodium borate, sodium chloride 0.7%, preserved with Thimerosal (Lilly) 0.001% and edetate disodium 0.1%). When lenses are disinfected with the chemical disinfection system, they may be stored in FLEXSOL® Sterile Disinfection and Storage Solution (sterile buffered isotonic solution of sodium chloride, sodium borate, boric acid, polyvinylpyrrolidone, polyoxyethylene and polyoxypropylene, preserved with Thimerosal (Lilly) 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

Only the above solutions and the following may be used with **Permalens®** Hydrophilic Contact Lenses:

1. PREFLEX® Sterile Cleaning Solution (sterile solution of a nonionic cleaner preserved with Thimerosal (Lilly) 0.004% and edetate disodium 0.2%).
2. NORMOL® Sterile Rinsing Solution (sterile buffered isotonic aqueous solution of sodium chloride, sodium borate and boric acid, preserved with Thimerosal (Lilly) 0.001%, edetate disodium 0.1% and chlorhexidine 0.005%).
3. CLERZ® Lubricating and Rewetting Eye Drops (sterile solution preserved with edetate disodium 0.1% and Thimerosal (Lilly) 0.001%).
4. ADAPETTES® Sterile Lubricating Solution (buffered isotonic aqueous solution containing Adsorbobase® (polyvinylpyrrolidone with other water-soluble polymers), Thimerosal (Lilly) 0.004%, and edetate disodium 0.1%).

No conventional (hard) contact lens solution should be used. Only those solutions specifically recommended by your eye-care practitioner should be used during wear.

WEARING RESTRICTIONS

Permalens® (perfilcon A) Hydrophilic Contact Lenses should not be worn while swimming or in the presence of noxious or irritating vapors.

Lens-Care Regimen

Patients must adhere to the recommended lens-care regimen of **Permalens®** Hydrophilic Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections which might result in corneal ulcers.

PRECAUTIONS

Storage

Permalens® Hydrophilic Contact Lenses must be stored in the appropriate storage solution: PERMASOL™ Rinsing and Storage Solution, BOILnSOAK® Sterile Saline Solution, or FLEXSOL® Sterile Disinfection and Storage Solution, depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in one of the following until it returns to a hydrated (soft) pliable state:

1. PERMASOL™ Rinsing and Storage Solution
2. BOILnSOAK® Sterile Saline Solution
3. FLEXSOL® Sterile Disinfection and Storage Solution

PERMA-case™ Contact Lens Storage and Carrying Case should be used for storing lenses.

Hygiene

Hands must be washed and rinsed thoroughly, and dried before handling the lenses. Cosmetics, lotions, soaps and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Cleaning and Disinfecting

Prior to wearing, **Permalens®** (perfilcon A) Hydrophilic Contact Lenses must be both cleaned and disinfected.

Cleaning: Monthly removal for cleaning is recommended. However, at the discretion of the eye-care practitioner, the lenses may be removed at a frequency adjusted to the needs of each patient. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Sterile Cleaning Solution. Between regular cleaning periods, CLERZ® Lubricating and Rewetting Eye Drops or ADAPETTES® Sterile Lubricating Solution may be used to maintain lens hydration while being worn.

Routine Thermal Disinfection Method: Permalens® Hydrophilic Contact Lenses may be effectively disinfected using a low-heat disinfecting unit approved for use with hydrophilic contact lenses. After cleaning with PREFLEX® Sterile Cleaning Solution, rinse lenses with PERMASOL™ Rinsing and Storage Solution or BOILnSOAK® Sterile Saline Solution, and disinfect in a RINCON® low-heat Thermal Disinfection Unit or other approved unit. The lens storage containers must be emptied and filled with fresh PERMASOL™ Rinsing and Storage Solution or BOILnSOAK® Sterile Saline Solution just prior to disinfecting the lenses.

Alternate Thermal Disinfection Method: If a thermal unit is not available, the following disinfecting system can be used temporarily. After cleaning the lenses according to instructions, fill each chamber of the PERMA-case™ with PERMASOL™ or BOILnSOAK.® Bring a pan of water to a rolling boil. Remove the pan from heat. Place the sealed carrying case into hot water and allow to cool. When the water is cool, lenses have been disinfected.

NOTE: USE OF THE RINCON® THERMAL DISINFECTION UNIT SHOULD BE RESUMED AS SOON AS POSSIBLE.

Chemical Disinfection Method: Disinfection with PREFLEX® Sterile Cleaning Solution, FLEXSOL® Sterile Disinfection and Storage Solution and NORMOL® Sterile Rinsing Solution has been shown to be an effective disinfection system. Following each removal, **Permalens®** Hydrophilic Contact Lenses must be cleaned with PREFLEX® Sterile Cleaning Solution and rinsed with NORMOL® Sterile Rinsing Solution. Each time the lens is stored, the PERMA-case™ Contact Lens Storage and Carrying Case must be emptied and refilled with fresh FLEXSOL® Sterile Disinfection and Storage Solution. Fresh FLEXSOL® Sterile Disinfection and Storage Solution must also be used when disinfecting a lens.

WARNING: FLEXSOL® STERILE DISINFECTION AND STORAGE SOLUTION SHOULD *NEVER* BE USED WIT

LENS EJECTION

Occasionally, a lens may become partially dehydrated du sleep. This may result in the lens being dislodged from th lid action or rubbing the eyelids. Dislodged or routinely re lenses should be thoroughly rehydrated in one of the foll solutions:

1. PERMASOL™ Rinsing and Storage Solution
2. NORMOL® Sterile Rinsing Solution
3. BOILnSOAK® Sterile Saline Solution

After the lens returns to a soft, supple state it should be cl and disinfected prior to replacement on the eye.

ADVERSE REACTIONS

Serious corneal damage may result from wearing lenses have been soaked in conventional hard contact lens solu Eye irritation may occur within a short time after putting c stored in a solution of improper pH or tonicity. Removal o lens will relieve the irritation.

Excessive tearing or redness, unusual eye secretions, re visual acuity, and photophobia are not normal; if these sy occur, the patient should be examined by an eye-care pra to determine the cause.

DOSAGE AND ADMINISTRATION

Fitting

Conventional methods of fitting contact lenses do not ap **Permalens®** (perfilcon A) Hydrophilic Contact Lenses. Fo detailed description of the fitting technique, refer to the P **lens®** Hydrophilic Contact Lens Professional Fitting Guid copies of which are available from Cooper Laboratories, I N. Whisman Road, Mountain View, California 94043.

WEARING SCHEDULE

Permalens® Hydrophilic Contact Lenses are indicated fo extended-wear (24-hour) use, without a gradual daily incr wearing time required. Cleaning is recommended at mon intervals. However, at the discretion of the eye-care prac the lenses may be removed at a frequency adjusted to th of each patient.

Lens Care and Handling

Care must be taken on the initial visit to ensure that the p is supplied with all necessary accessory products and full stands all care and handling instructions for the lenses. R post-fitting visits are necessary to assure patient health a compliance with instructions.

HOW SUPPLIED

Each lens is supplied sterile in a sealed glass vial contain a buffered isotonic salt solution. The vial is marked with th dioptric power, base curve, diameter, lot number, and exp date of the lens.

Accessories

Patient Care Kit	Cat.
Wearer's Manual	Cat.
PERMA-case™ Contact Lens Storage and Carrying Case	Cat.
FLEXSOL® Sterile Disinfection and Storage Solution*	Cat.
NORMOL® Sterile Rinsing Solution*	Cat.
PREFLEX® Sterile Cleaning Solution*	Cat.
CLERZ® Lubricating and Rewetting Eye Drops	Cat.
PERMASOL™ Rinsing and Storage Solution	Cat.
RINCON® Thermal Disinfection Unit**	Cat.
BOILnSOAK® Sterile Saline Solution*	Cat.
ADAPETTES® Sterile Lubricating Solution	Cat.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

[1]Fatt I, Morris JA: A survey of gas-permeable contact lenses. *The Optician:* 27-36 (November 4, 1977).

*A product of Burton, Parsons & Company, Inc.
**A product of Rincon Industries, Inc.

Cooper

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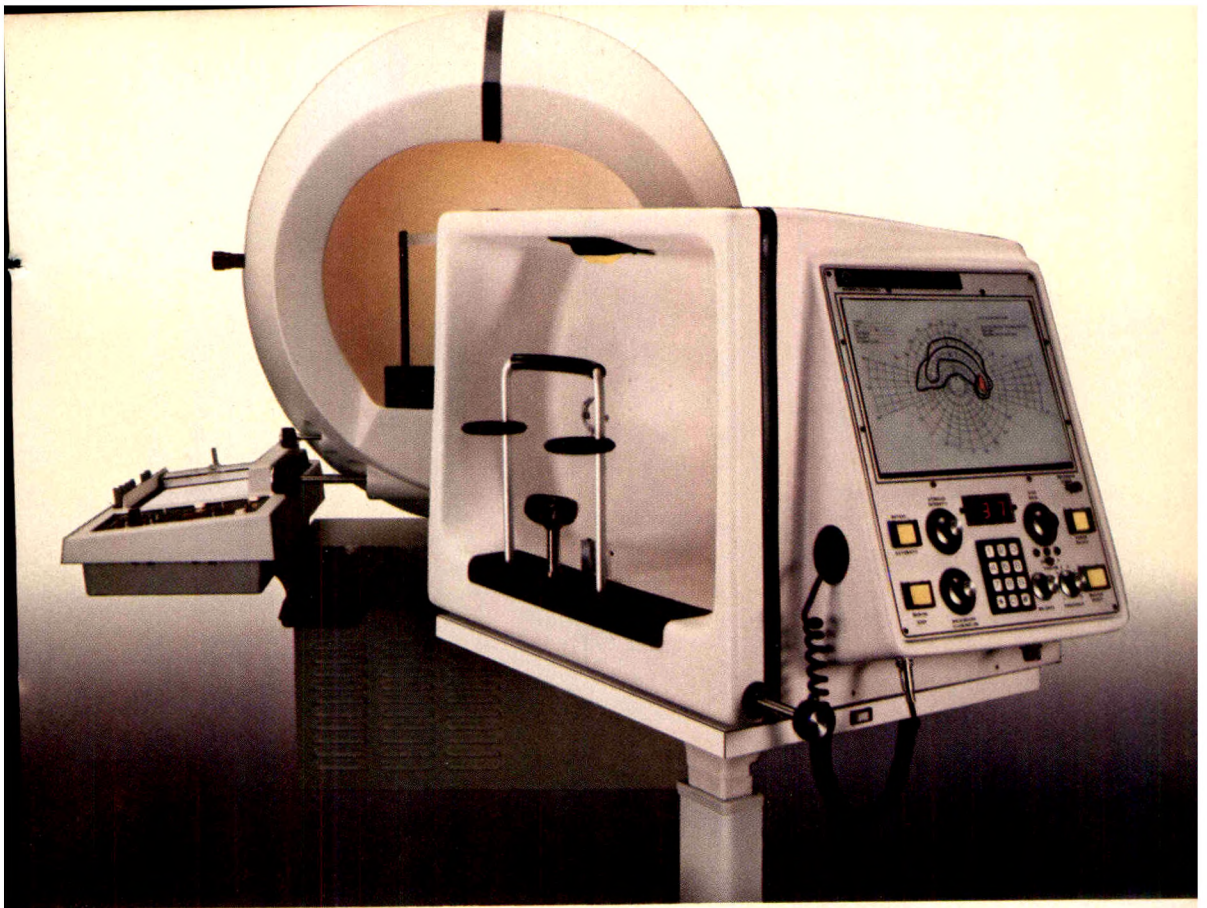

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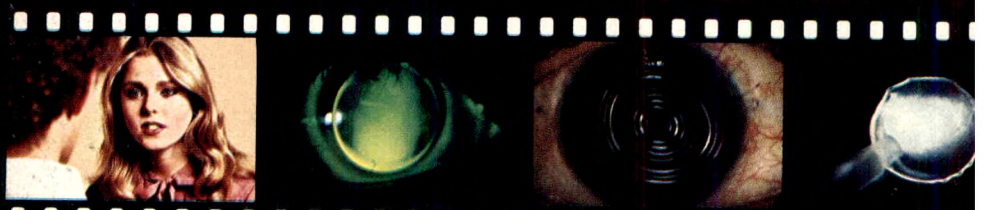

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Brief Summary
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The POLYCON contact lens is indicated for the correction of visual acuity for persons with nondiseased eyes having ametropias, including those with high degrees of corneal or refractive astigmatism, as well as aphakia.

CONTRAINDICATIONS
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WARNINGS
(1) If the lens becomes less comfortable to the wearer than when first placed on the wearer's cornea, a foreign body may be present. The patient should remove the lens immediately. If discomfort persists, an eye care practitioner should examine the patient as soon as possible to determine if any corneal abrasion, ulceration, irritation or infection is present.

(2) Aphakic patients should not be fitted during the postoperative period until the surgeon determines that the eye has healed completely.

(3) Only use Preflex® Sterile Cleaning Solution, Flex-Care® Sterile Solution, and Adapettes® Sterile Lubricating Solution with the POLYCON lens. Store ONLY in Flex-Care® Sterile Solution. Patients must adhere to recommended daily lens care regimen. FAILURE TO DO SO MAY RESULT IN DEVELOPMENT OF SERIOUS OCULAR INFECTIONS.

(4) Wearers must not use any medicaments or ophthalmic solutions other than Adapettes® solution prior to inserting the lens or while the lens is on the eye.

(5) Remove before sleeping or in the presence of noxious and irritating vapors.

PRECAUTIONS
THE POLYCON CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER. To disinfect the lens, it is stored in fresh Flex-Care® solution for a minimum of four hours daily in the patient lens storage case. After removal of the lens from the storage case, rinse the lens thoroughly with Flex-Care® solution and apply Adapettes® lubricating solution to the lens surfaces as a wetting agent prior to inserting the lens in the eye.

ADVERSE REACTIONS
Rainbows or halos around objects or blurring of the vision. Excessive tearing, unusual eye secretions, and photophobia.

Preflex,® Flex-Care® and Adapettes® are trademarks of Burton, Parsons & Company, Inc.

1-80

References

1 Multi-clinic study of 418 patients, data on file, Syntex Ophthalmics, Inc.

2 Korb JE, Finnemore VM: Corneal edema with polymethylmethacrylate vs. gas-permeable rigid polymer contact lenses of identical design. To be published.

3 Williams CE: New design concepts for permeable rigid contact lenses. *JAOA* 50:331-336, 1979.

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Ointment-Sterile

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- **Single-entity antibiotic.**
- **Generally low potential for sensitivity reactions and irritation.**

DESCRIPTION Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN **Ophthalmic Solution** is a sterile, aqueous solution buffered to approximately pH 7 for use in the eye. Each ml. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN **Ophthalmic Ointment** is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg. gentamicin) in a bland base of white petrolatum, with methylparaben and propylparaben as preservatives.

ACTIONS The gram-positive bacteria against which gentamicin sulfate is active include coagulase-positive and coagulase-negative staphylococci, including certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci; and *Diplococcus pneumoniae*. The gram-negative bacteria against which gentamicin sulfate is active include certain strains of *Pseudomonas aeruginosa*, indole-positive and indole-negative *Proteus* species, *Escherichia coli*, *Klebsiella pneumoniae* (Friedlander's bacillus), *Haemophilus influenzae* and *Haemophilus aegyptius* (Koch-Weeks bacillus), *Aerobacter aerogenes*, *Moraxella lacunata* (diplobacillus of Morax-Axenfeld), and *Neisseria* species, including *Neisseria gonorrhoeae*. Although significant resistant organisms have not been isolated from patients treated with gentamicin at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

INDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

CONTRAINDICATIONS GARAMYCIN **Ophthalmic Solution** and **Ointment** are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS GARAMYCIN **Ophthalmic Solution** is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye.

PRECAUTIONS Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms, such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

Ophthalmic ointments may retard corneal healing.

ADVERSE REACTIONS Transient irritation has been reported with the use of GARAMYCIN **Ophthalmic Solution.**

Occasional burning or stinging may occur with the use of GARAMYCIN **Ophthalmic Ointment.**

DOSAGE AND ADMINISTRATION GARAMYCIN **Ophthalmic Solution:** instill one or two drops into the affected eye every four hours. In severe infections, dosage may be increased to as much as two drops once every hour.

GARAMYCIN **Ophthalmic Ointment:** apply a small amount to the affected eye two to three times a day.

HOW SUPPLIED GARAMYCIN **Ophthalmic Solution—Sterile,** 5-ml. plastic dropper bottle, sterile, boxes of one and six. Store away from heat.

GARAMYCIN **Ophthalmic Ointment—Sterile,** ⅛-ounce tube, boxes of one and six. Store away from heat.

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cute catarrhal conjunctivitis
episcleritis. Etiology: S. aureus.
Before treatment.

7th day post treatment with
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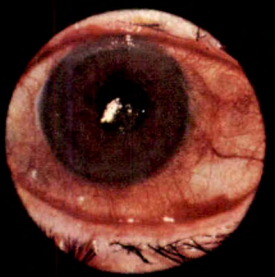
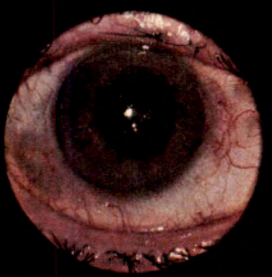
Culture negative.

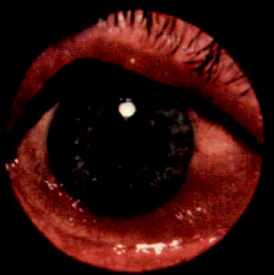
Corneal ulcer.
Etiology: S. aureus.
Before treatment.



17th day post treatment with
GARAMYCIN Ophthalmic.
Culture negative.



Acute hemorrhagic conjunctivitis.
Etiology: Pneumococcus.
Before treatment.



4th day post treatment with
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Culture negative.

Corneal marginal ulcer.
Etiology: S. aureus.
Before treatment.

10th day post treatment with
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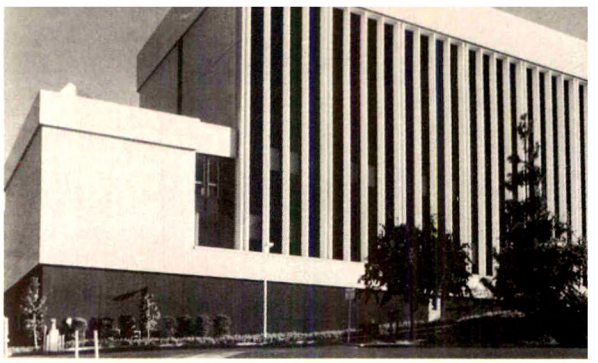

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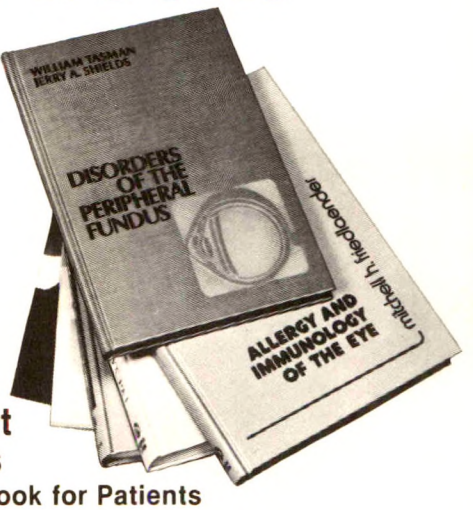

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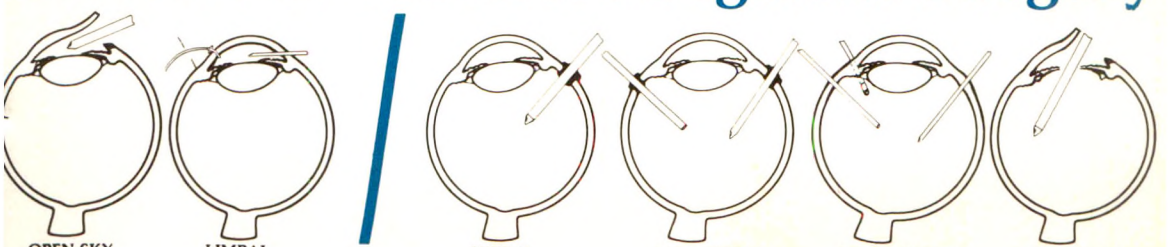

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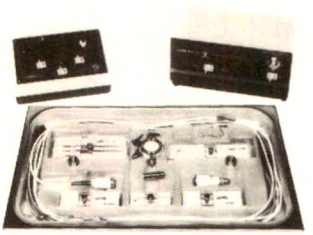

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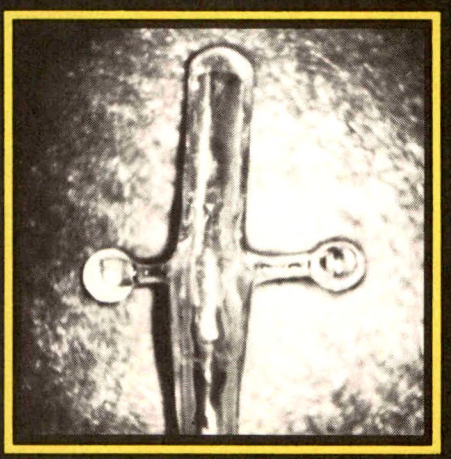

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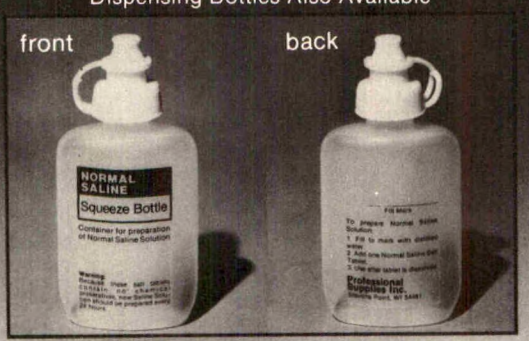

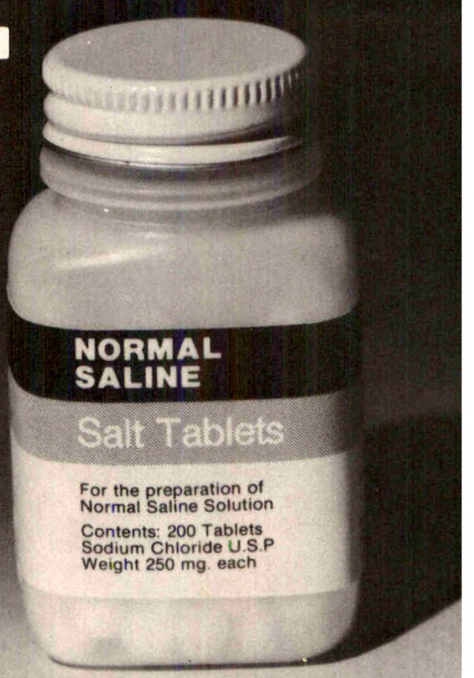

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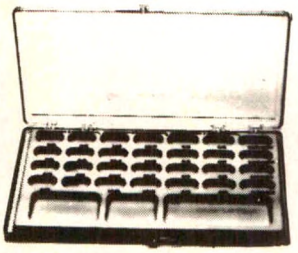

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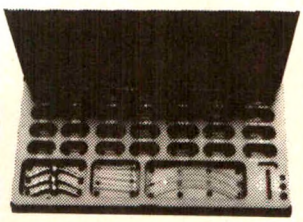

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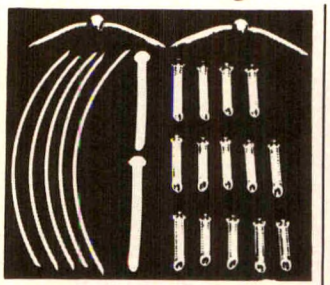

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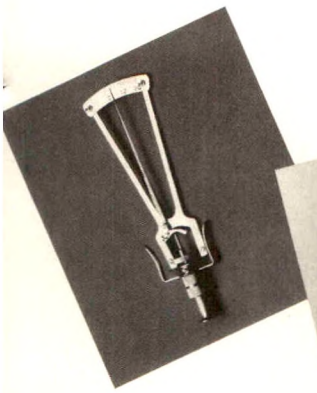

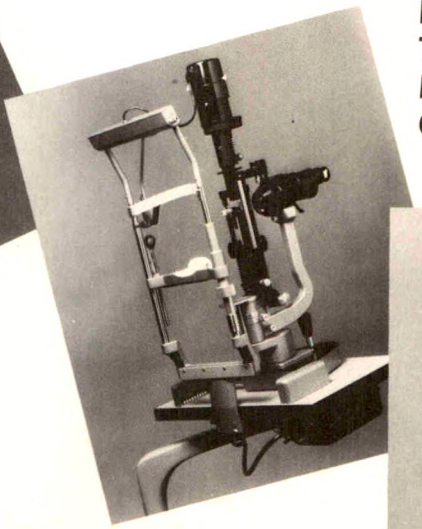

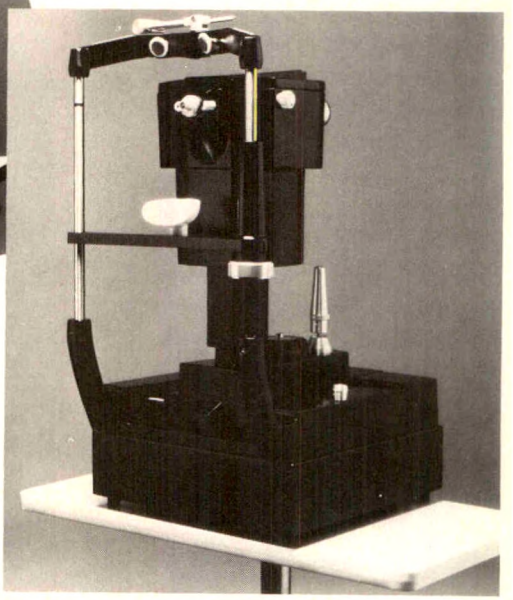

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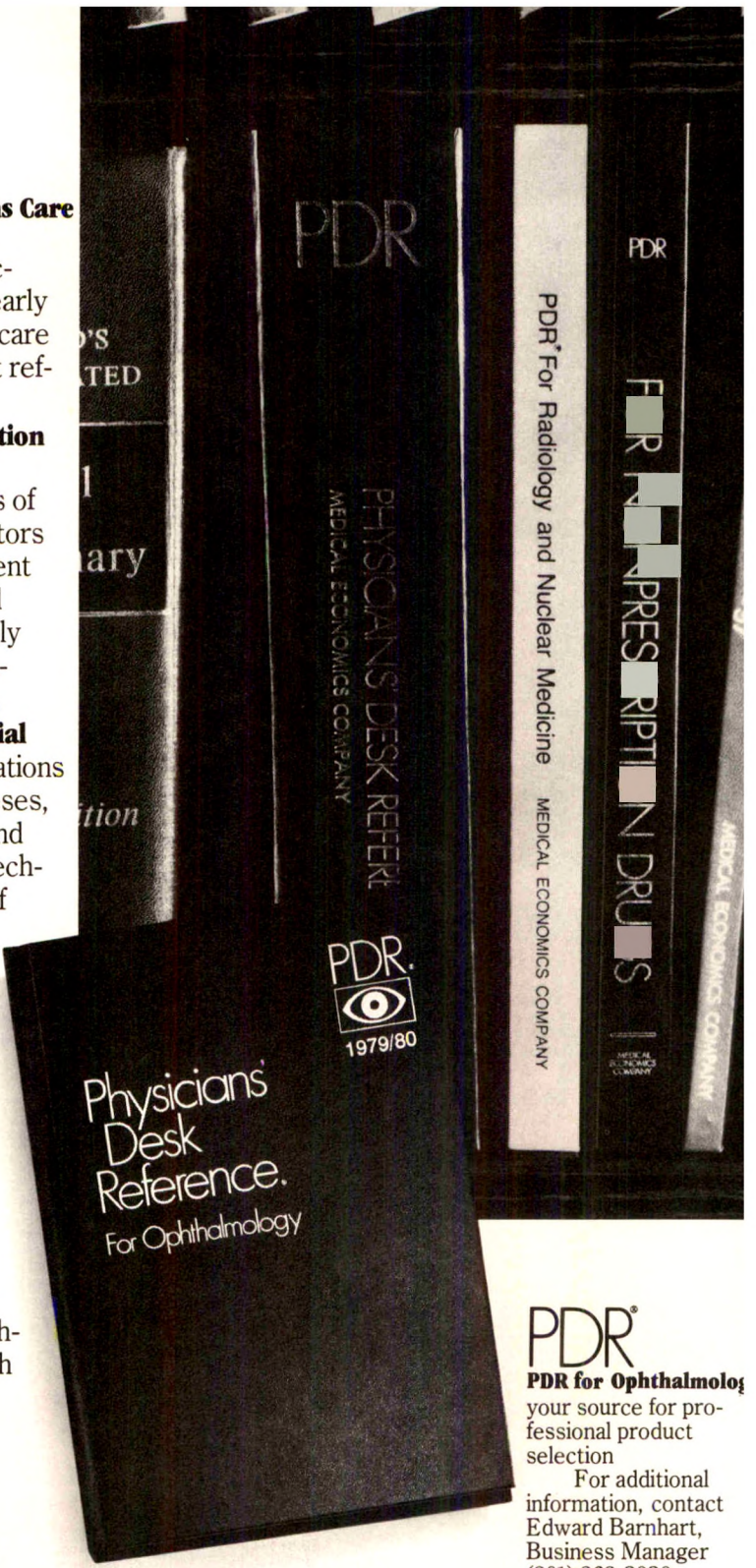

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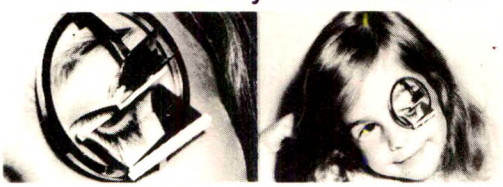

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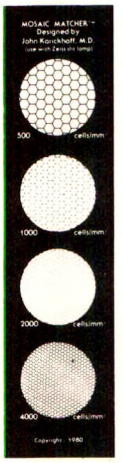

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For any further information, please contact Miss Katherine Sgabelloni, Coordinator Ophthalmic Services, Park Ridge Hospital, 1555 Long Pond Road, Rochester, New York 14626. Phone: (716) 225-7150, extension 4054.

The Clear Advantages of Topcon's New LM-P4

Topcon's newest lensmeter—the LM-P4—gives you three clear advantages over any instrument in its price range. Because of these benefits, the LM-P4 is unsurpassed in ease and accuracy when measuring all types of lenses.

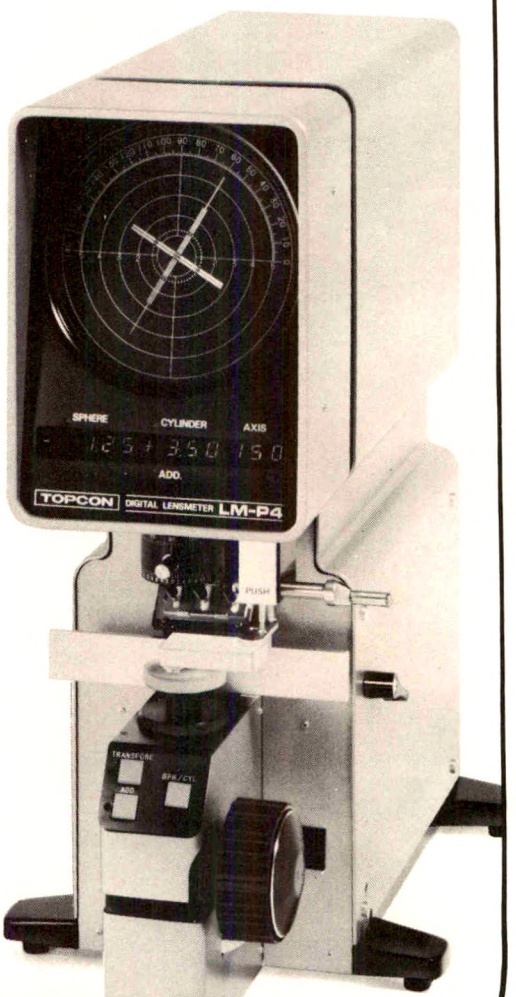
1. An illuminated *projection screen* features combined cross-hair and dot targets for your convenience; prevents both the accommodation and fatigue problems associated with monocular units.

2. An easy-to-read *digital display* eliminates the errors that can arise when taking subjective scale readings. Big, clearly illuminated numbers assure maximum accuracy.

3. Built-in *memory* microprocessor does away with the need for calculations. You can get all measurements directly in three fast, uncomplicated steps.

The LM-P4 is so simple and precise that you can teach your assistant to use it in minutes. And always be confident of the findings you are presented with. Best of all, the LM-P4 has a price that's easy on your equipment budget.

Ask your Topcon dealer for a demonstration. In just five minutes, the advantages should be clear to you.



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OCULOPLASTIC SURGICAL DISSECTION COURSE

(40 HRS. CME & CAT I)

May 14-17, 1980

OBJECTIVES:
An in-depth symposium to provide the practicing and resident surgeon with an Oculoplastic Course featuring LIVE SURGERY VIDEO TAPES, FILMS, LECTURES AND PARTICIPANT'S CADAVER SURGERY.

FACULTY:

L. Bergmann, M. D.
B. Cosman, M. D.
N. Cousins, Esq.
M. Dunn, M. D.
H. Gould, M. D.
M. Guibor, C. O.
P. Guibor, M. D.
S. Hecht, M. D.
L. Herman, PhD.
A. Messina, M. D.
E. Wiggs, M. D.
D. Wolfley, M. D.
and others.

SUBJECTS:
Cosmetic Blepharoplasty, Blepharoptosis, Trauma Surgery, Lid Reconstruction, Lacrimal Surgery, Orbital Reconstruction, Entropion, Ectropion, Orbital Fractures and Orbital Tumors.

May 14-17, 1980

OCULOPLASTIC REGISTRATION FORM
Registration $650

Name _____

Address _____

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Specialty: Ophth—ENT—Plastic—Derm
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Make check payable: The Oculoplastic Foundation, Inc. OCULOPLASTIC COURSE

COSMETIC FACIAL SURGICAL DISSECTION COURSE

(40 HRS. CME & CAT I)

May 17-20, 1980

OBJECTIVES:
A unique and practical surgical course, presented by multiple disciplines, covering FACIAL COSMETIC SURGERY and featuring PARTICIPANT'S CADAVER SURGERY.

FACULTY:
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Richard Coburn, M.D., PLASTIC
Norman L. Cousins, Esq., ATTORNEY
Pierre Guibor, M.D., OPHTH
Sanford Hecht, M.D., OPHTH
Norman Orentreich, M.D., DERM
Eugene Wiggs, M.D. OPHTH
Darrell Wolfley, M.D., OPHTH

SUBJECTS:
Face and Neck Lifting, Cosmetic Belpharoplasty, Brow and Forehead Lifting, Rhino plasty, Otoplasty, Mentoplasty, Dermabrasion and Chemical Peel, Hair Transplantation, Scar Revision, Grafts, Flaps and Camouflage.

May 17-20, 1980
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Registration $800

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Specialty: Ophth—ENT—Plastic—Derm
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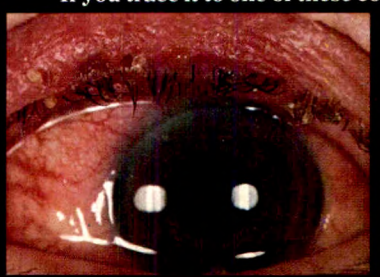
Make check payable: The Oculoplastic Foundation, Inc. COSMETIC FACIAL COURSE

Clip and mail with registration fee: Ms. Paula Tamkin, Registrar
c/o Dr. P. Guibor, 630 Park Avenue
New York, N. Y. 10021 (212) 734-1010

The infected eye

If you trace it to one of these common problems...



*Acute bacterial conjunctivitis**
Marked by itching or burning, hyperemia, lid edema and lacrimation or purulent discharge. Second only to refractive errors in frequency among ocular complaints.

*Bacterial corneal ulcer**
Pain, photophobia, lacrimation and blepharospasm are usual presenting symptoms. Prompt institution of therapy is vital to avoid possible visual difficulty.

* When due to susceptible microorganisms.

Gantrisin® **sulfisoxazole diolamine/Roche**
Ophthalmic Solution, Ophthalmic Ointment

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Conjunctivitis, corneal ulcer, other superficial ocular infections due to susceptible microorganisms; as adjunct in systemic sulfonamide therapy of trachoma.

Contraindications: Hypersensitivity.

Precautions: Incompatible with silver preparations; inactivated by para-aminobenzoic acid in purulent exudates; may increase growth of nonsusceptible organisms, including fungi. Ointment may retard corneal healing. Discontinue use if undesirable reactions occur.

watch it respond to

Gantrisin®

sulfisoxazole diolamine

Ophthalmic Solution and Ophthalmic Ointment

Effective treatment for conjunctivitis, corneal ulcer and other infections due to susceptible microorganisms, such as *Staphylococcus aureus*

Ophthalmic Solution—a sterile, isotonic preparation containing 4% (40 mg/ml) sulfisoxazole diolamine—generally avoids significant stinging or burning

Ophthalmic Ointment—also containing 4% sulfisoxazole diolamine—provides more sustained contact with the ocular infection and is particularly appropriate for nighttime therapy

A Brief Summary of the product information, below, provides precautions and contraindications

Main photo taken with the Carl Zeiss photo slit lamp.

Dosage and Administration: Solution: 2-3 drops in eye 3 or more times daily. Take care not to contaminate dropper. Ointment: small amount in lower conjunctival sac 1-3 times daily and at bedtime.

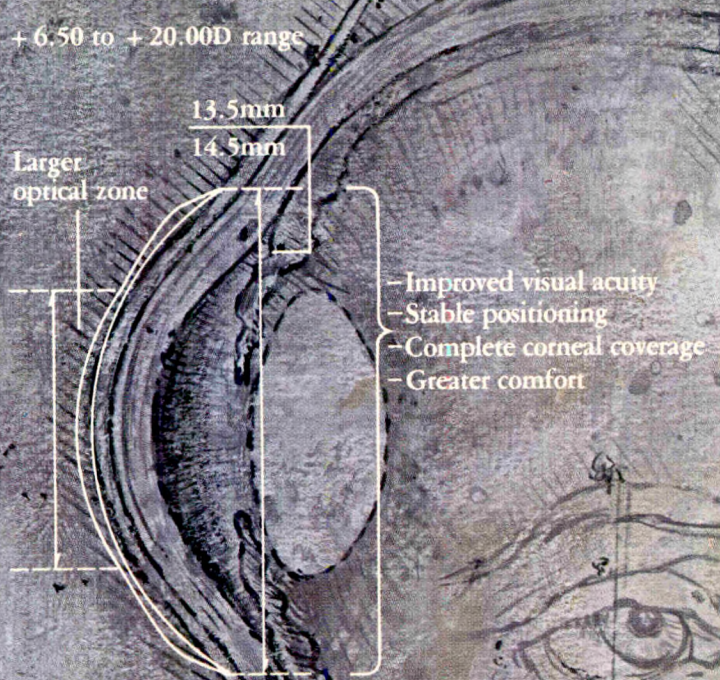
How Supplied:

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Bausch & Lomb Scientific Update:

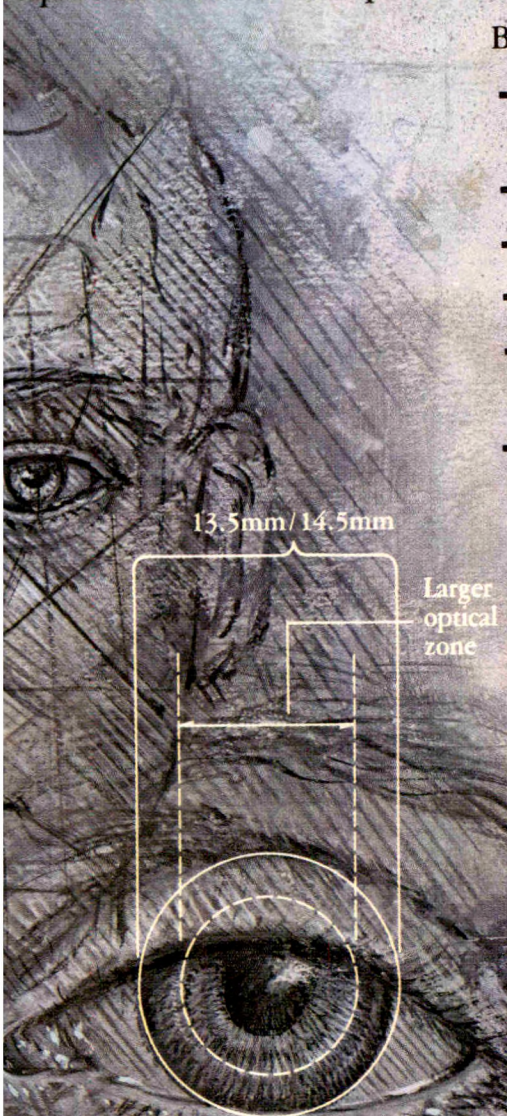
An Important New Plus for Your Aphakic Patients!



Improved Bausch & Lomb high plus lenses.

Now Bausch & Lomb's new +H3 and +H4 series offer you superior visual acuity, better corneal coverage and greater comfort than any of our older high plus series could provide.

With the H3 and H4 series, you can give more of your aphakic patients the comfort, safety and good vision soft contact lenses offer. You'll conserve time and expense because the H3 and H4 series are quickly fitted by the First Fit method. And they require far fewer follow-up visits than extended wear lenses.



Bausch & Lomb's improved high plus with:

- ++ Complete and stable coverage for superior acuity.
- ++ Increased patient comfort.
- ++ Durability—less tendency to tear.
- ++ Larger optical zone—now 13% larger.
- ++ Two diameters: H3, 13.5mm and H4, 14.5mm.
- ++ Powers from +6.50 to +20.00D.

Bausch & Lomb high plus lenses—improved to make fitting your aphakic patients easier. H3 and H4—only from the leader in soft lens science. Call your Bausch & Lomb representative for more information.

See next page for brief summary of prescribing information.

BAUSCH & LOMB
SOFLENS® (polymacon) Contact Lenses

The leader in soft lens science

BAUSCH & LOMB SOFLENS® (polymacon) Contact Lenses

BRIEF SUMMARY (For full prescribing information see package insert.)
VISION CORRECTION USE

INDICATIONS: SOFLENS Contact Lenses are indicated for vision correction use in persons with non-diseased eyes and in aphakia. **CONTRAINDICATIONS:** SOFLENS Contact Lenses are contraindicated in the presence of any active untreated infection or abnormality of the anterior segment of the eye. **WARNINGS: Abrasions and Infections**—If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present or any abnormal eye condition is observed concurrent with lens wear, the lens should be removed immediately and a physician consulted. **Aphakic Patients:** Aphakic patients should not be fitted with SOFLENS Contact Lenses during the postoperative period until, in the opinion of the surgeon, the eye has healed completely. **Lens Care and Handling:** Persons who require only vision correction and who would not, or could not adhere to the recommended daily care of SOFLENS Contact Lenses or who are unable to place and remove the lenses should not be provided with them. Failure to follow handling and cleaning instructions could lead to serious eye infections which might result in corneal ulcers. Malfunction and rusting of the metal interior of the BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) as well as discoloration and cracking of the lens case has been reported after varying periods of use. If such occurs, appropriate replacement is indicated to avoid interference with the disinfection procedure. Keep the BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) and II (ASEPTRON™) clean and dry at all times. **Medicants and Eye Drops:** When the lenses are used by persons requiring only vision correction no ophthalmic solutions or medicants should be used. No conventional (hard) contact lens solutions and eye drops, except BAUSCH & LOMB™ Lens Lubricant should be used by SOFLENS Contact Lens wearers prior to placement, or while the lens is in place, on the eye. Also, no solutions, including conventional (hard) contact lens solutions should be used. Only daily cleaner, lens lubricant, saline, and the solution made from the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets are to be used on a SOFLENS Contact Lens when the lens is off the eye. **Wearing Restrictions:** SOFLENS Contact Lenses when used only for vision correction should be removed before sleeping or swimming and in the presence of noxious and irritating vapors. Insufficient lacrimal secretions or hypoesthesia may be restricting factors to the wearing of soft contact lenses. **PRECAUTIONS: Storage**—SOFLENS Contact Lenses must be stored ONLY in saline solution or BAUSCH & LOMB™ Sterile Disinfecting Solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be resoaked in saline solution or BAUSCH & LOMB™ Sterile Disinfecting Solution until it returns to its soft, pliable state which may take as long as forty minutes. Saline solution must be used DAILY for cleaning, storing, and disinfection of lenses. The carrying case must be emptied and refilled with fresh saline solution just before disinfecting the lenses. **Lens Handling:** Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses. Cosmetics, lotions, soaps, and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled. A SOFLENS Contact Lens may be damaged by nicking or tearing if care is not exercised during placement on or removal from the eye, replacing or removing it from the carrying case or in the cleaning process. **Disinfecting:** Saline solution must be used DAILY for cleaning, storing, and disinfection of lenses. After removal from the eye, the SOFLENS Contact Lens must be rubbed gently with Daily Cleaner then rinsed with saline solution to remove mucus and film from the lens surface. The BAUSCH & LOMB™ Lens Carrying Case (LENSGARD™) must be emptied and refilled ⅔ full with fresh saline solution just before disinfecting the lenses and must always be tightly closed to prevent leakage of saline from the case and subsequent dehydration of the lenses. In order to remove protein deposits which may form on the lenses, wearers should use the SOFLENS™ Enzymatic Contact Lens Cleaning Tablets according to the directions for use which accompany the tablets. To help remove tear residues and mucus as well as other deposits that tend to accumulate on the lens surface, patients should use Daily Cleaner according to the directions for use which accompany the product. Disinfecting with a BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) or II (ASEPTRON™) is necessary to kill microorganisms. If a BAUSCH & LOMB™ Disinfecting Unit I (ASEPTOR®) or II (ASEPTRON™) is not available, lenses may be disinfected by immersing your lenses in BAUSCH & LOMB™ Saline Solution in the carrying case and dropping the sealed case into a pan of already boiling water. Remove the pan from heat after ten minutes and allow the water to cool before removing your lenses. When this boiling method of disinfection is used, the lenses can be damaged if the boiling water is allowed to completely evaporate. Chemical disinfection with BAUSCH & LOMB™ Sterile Disinfecting Solution has been tested microbiologically and shown to be an effective disinfection procedure for the SOFLENS hydrophilic contact lens. If chemical disinfection is used the SOFLENS hydrophilic contact lens must be cleaned and rinsed daily with BAUSCH & LOMB™ Sterile Daily Cleaner and BAUSCH & LOMB™ Sterile Disinfecting Solution. The lens carrying case must be emptied and refilled with fresh BAUSCH & LOMB™ Sterile Disinfecting Solution prior to disinfecting the lens. Fresh BAUSCH & LOMB™ Sterile Disinfecting Solution must be used daily for storing and disinfecting the lens. **WARNING:** BAUSCH & LOMB™ STERILE DISINFECTING SOLUTION SHOULD NOT BE USED WITH HEAT. **Fluorescein:** Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with sterile normal saline solution and wait at least one hour before replacing the lenses. Earlier replacement may cause the lenses to absorb residual fluorescein. **ADVERSE REACTIONS:** Serious corneal damage may result from wearing a SOFLENS Contact Lens which has been soaked in a conventional contact lens solution. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation. A lens adheres very rarely to an eye as a result of sleeping with the lens on, or wearing a hypotonic lens. If a lens adheres for any reason, apply fresh saline and wait until the lens moves freely before removing it. Clinical studies indicate that corneal edema, as manifested by symptoms such as rainbows, halos around lights, or foggy vision, may occur in less than 5% of SOFLENS Contact Lens wearers. If these symptoms occur, the lenses should be removed and professional consultation obtained. Excessive tearing, unusual eye secretions, and photophobia are not normal. If these symptoms occur, the patient should be examined to determine their cause. Neovascularization of the cornea has been observed in some aphakic patients fitted with the SOFLENS Contact Lens, which may require discontinuation of the lens. Medical consultation should be obtained in such an instance.

4/80

BAUSCH & LOMB
SOFLENS DIVISION
Rochester, New York 14602

INTRAOCULAR LENS IMPLANTATION UPDATE

St. Mary's Hospital, Montreal
in cooperation with
The Canadian Implant Association (CIA)
Hotel Lowes "La Cite"
3625 Park Avenue
Montreal Canada
Saturday June 21, 1980

Speakers

James Aquevella, M.D. .....Rochester
Herve Byron, M.D. .....New Jersey
Miles Galin, M.D. .....New York
Jack Hartstein, M.D. .....St. Louis
Kenneth Barasch, M.D. .....New York
Peter Choyce, M.D. .....London
Marvin Kwitko, M.D. .....Montreal
Stephen Shearing, M.D. .....Las Vegas

This seminar will cover the latest advances in lens implant surgery including lens power calculation, sterility and toxicity studies of implant plastics, implant techniques including angle supported, iris supported and capsule supported lenses (Binkhorst, Choyce, Glass, Federov, Shearing, etc.). Most of the speakers who have been implant surgeons for over a decade will discuss indications, surgical techniques and management for short and long term complications of the various lenses.

Registration Fee $125.00 (Residents $50.00)

For information write,
Marvin L. Kwitko, M.D., Program Chairman
5591 Cote des Neiges Rd.
Montreal, Quebec Canada
H3T 1Y8

PUERTO RICO OPHTHALMOLOGICAL SOCIETY

ANNUAL CONVENTION

October 10-13, 1980
CARIBE HILTON HOTEL
SAN JUAN, PUERTO RICO

GUEST SPEAKERS:
Myles Behrens, M.D.
Jorge Buxton, M.D.
Joseph Calhoun, M.D.
Joseph Flanagan, M.D.
Allan E. Kolker, M.D.
Dennis Shepard, M.D.
B. D. Srinivasan, M.D.

FOR INFORMATION:
Manuel A. López de Victoria, M.D.
P.O. Box 10431
Caparra Heights, Puerto Rico 00922
Telephone: (809) 781-3022

C.M.E.—15 HRS — CATEGORY I

REGISTRATION FEE:—$150.00

Miniphage: 1.05mm Diameter With Built in Infusion

The DKS Miniphage is still the only miniature cutting head that offers infusion built in, not added on. The 1.05mm, diameter tip is a disposable, sharp and versatile cutting instrument guaranteed every time.

Two models are available: The V3001-120, with finger hole control of suction; and the V3001-124, with foot switch control of suction and positive shut-off.

Use of the V3001-124 will require modification to existing systems in the field. New systems are available with or without modification.

Now available in the new DKS disposable sterile pack.

One of a family of DKS precision disposable surgical instruments.

A product of David Kopf Instruments
7327 Elmo St., Tujunga, CA 91042
Telephone: (213) 352-5955
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DKS

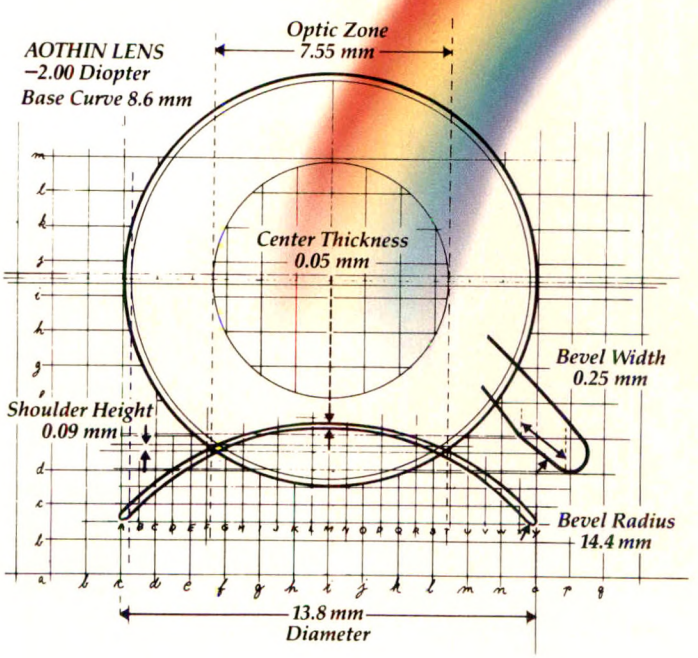
Ready When You Are

TO BRING MORE OXYGEN TO THE CORNEA, AO BRINGS YOU

NEW AOTHIN™

(TETRAFILCON A)

SOFT CONTACT LENS



THE THIN SOFT LENS WITH A CONSISTENTLY THIN CARRIER

With some other thin soft lenses, portions of the lens periphery are just as thick as with a standard soft lens. Yet overall, the thickness of a soft lens may be the most frequent cause of corneal edema.[1] So we've developed a thin soft lens with a carrier that's consistently thin throughout, even in high minus powers, for consistently good oxygen exchange.

Of course, the new AOTHIN lens offers you all you've come to expect from an American Optical lens. Excellent visual acuity, durability and ease of handling. With a simple set of lens parameters: one diameter (13.8 mm), three base curves (8.3, 8.6 and 9.0 mm) and a minus range of -0.25D to -7.75D in .25 diopter steps. For further details, please contact your American Optical representative or American Optical Soft Contact Lens Distributor TODAY!

Please see next page for full prescribing information.

Reference:
[1]Mandell RB: The "tight" soft contact lens. *Contact Lens Forum*, December, 1979, pp 21-32.

American Optical Corp.
VISION CARE PRODUCTS
SOUTHBRIDGE, MA 01550

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TO BRING MORE OXYGEN TO THE CORNEA

NEW AOTHIN™

(TETRAFILCON A)

SOFT CONTACT LENS

AOTHIN™ (tetrafilcon A) Soft Contact Lens

DESCRIPTION: AOTHIN™ (tetrafilcon A) Soft Contact Lens is a hemispherical shell which covers the cornea and may cover a portion of the adjacent sclera. The lens material, tetrafilcon A, is a hydrophilic random terpolymer of 2-hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone and methylmethacrylate. The polymer is a three-dimensional network of terpolymer chains joined by divinylbenzene cross-links. It consists of 57.5% tetrafilcon A and 42.5% water by weight when fully hydrated in 0.9% sodium chloride solution buffered with monobasic and dibasic sodium phosphates.

ACTIONS: In its hydrated state, the AOTHIN™ Soft Contact Lens is soft and pliable. When dry, the lens becomes hard and brittle. These states are completely reversible and a lens which has been permitted to dry out will recover all of its hydrated properties when placed in normal saline for a period of two hours. When placed on the human cornea, the hydrated lens acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

INDICATIONS: AOTHIN™ Soft Contact Lenses are indicated for the correction of vision in persons with non-diseased eyes who have spherical ametropias, corneal astigmatism of 2.50 diopters or less and/or refractive astigmatism of 2.00 diopters or less.

CONTRAINDICATIONS: AOTHIN™ Soft Contact Lenses are contraindicated in the presence of any of the following conditions: (1) Acute and subacute inflammation of the anterior segment of the eyes. (2) Any eye disease which affects the cornea and conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.

WARNINGS: Medications and Eye Drops: AOTHIN™ Lenses must be stored in an appropriate solution when off the eyes, the type of solution being dependent on the system used for disinfection. When the lenses are disinfected with the thermal disinfection system, they may be stored *only* in LENSRINS® or BOIL n SOAK® Solution (sterile, buffered preserved saline solution). When lenses are disinfected with the chemical disinfection system, they may be stored *only* in FLEXSOL® Solution (sterile, isotonic buffered solution containing Adsorbobase — a water soluble polymeric vehicle — and preserved with thimerosal 0.001%, chlorhexidine 0.005% and edetate disodium 0.1%).

No ophthalmic solutions or medications, including hard contact lens solution, can be used by AOTHIN™ Lens wearers prior to or while the lenses are in place on the eyes. Also, no solutions, including hard contact lens solutions, other than LENSRINS® or BOIL n SOAK® Solution or FLEXSOL® Solution may be used on AOTHIN™ Lenses when they are off the eyes.

Since liquids and vapors may be absorbed by AOTHIN™ Lenses, they should not be placed in the mouth for wetting, nor wiped with a cloth or tissue.

Abrasions and Infections: If a lens becomes less comfortable than it was when first placed on the wearer's cornea, the lens should be removed immediately and the wearer's eye and the lens examined for the possible presence of a foreign body. If any eye abrasion, ulceration, irritation or infection is present, or any abnormal eye condition is observed concurrently with lens wear, the lens should be removed immediately and a physician consulted.

Wearing Restrictions: AOTHIN™ Soft Contact Lenses should not be worn while swimming, sleeping, or in the presence of irritating fumes or vapors.

Visual Blurring: If visual blurring occurs, the lens must be removed until the condition subsides.

Lens Sanitation: Patients must adhere to the recommended daily sanitary care procedures for AOTHIN™ Soft Contact Lenses. Failure to follow this procedure may result in the development of serious ocular infections.

PRECAUTIONS: Storage: AOTHIN™ Lenses may be stored *only* in the appropriate storage solution: LENSRINS® or BOIL n SOAK® Solution or FLEXSOL® Solution depending on disinfecting methods used. If left exposed to air, the lenses will dehydrate, become brittle and break readily. If a lens dehydrates, it should be soaked in either LENSRINS® BOIL n SOAK® or FLEXSOL® Solution until it returns to a soft, supple state.

Cleaning and Disinfecting: AOTHIN™ Lenses must be both cleaned and disinfected daily. Separate procedures and products are needed to clean and to disinfect. Two methods of disinfection, thermal or chemical, have been shown to be equally effective. The choice of disinfection system should be made in consultation with your eye care practitioner.

Cleaning: Daily cleaning is necessary to remove mucus and other deposits which may have accumulated on the lens surface. Each time the lenses are removed from the wearer's eyes, both surfaces of the lenses must be cleaned using several drops of PREFLEX® Cleaning Solution (sterile solution of a nonionic cleaner preserved with thimerosal 0.004% and edetate disodium 0.2%). Lenses must be cleaned before they are disinfected, as deposits on the lenses tend to harden and become more difficult to remove after the lenses are disinfected.

Disinfecting: AOTHIN™ Soft Contact Lenses may be disinfected with either a thermal or chemical regimen. One method or the other must be selected, but not both. THE USER MUST NOT ALTERNATE BETWEEN METHODS.

Thermal Disinfection Method: AOTHIN™ Lenses may be effectively disinfected using a disinfecting unit approved for use with tetrafilcon A hydrophilic contact lenses. After cleaning with PREFLEX® Cleaning Solution, rinse lenses with LENSRINS® or BOIL n SOAK® solution and disinfect in an approved thermal disinfection unit. The lens storage containers must be emptied and filled with fresh LENSRINS® or BOIL n SOAK® solution just prior to disinfecting the lenses.

Alternate Thermal Disinfection Method: If a thermal unit is not available, the following disinfection system can be used temporarily. After cleaning the lenses according to instructions, fill the lens storage container with fresh LENSRINS® or BOIL n SOAK® solution. Bring a pan of water to a rolling boil. Remove the pan from heat. Place the tightly sealed lens storage container into the hot water and allow to cool. When the water is cool, lenses have been disinfected.

NOTE: Use of an approved thermal disinfection unit should be resumed as soon as possible.

Chemical Disinfection: Disinfection with PREFLEX® Cleaning Solution, FLEXSOL® Solution and NORMOL® Rinsing Solution (sterile isotonic saline solution preserved with thimerosal 0.001% and chlorhexidine 0.005%) has also been shown to be an effective disinfection system for daily care of AOTHIN™ (tetrafilcon A) Soft Contact Lenses.

AOTHIN™ Lenses must be cleaned and rinsed daily (or after wearing) with PREFLEX® Cleaning Solution and NORMOL® Rinsing Solution. The FLEXKIT Lens Case must be emptied and refilled with fresh FLEXSOL® Solution each time the lens is stored. Fresh FLEXSOL® Solution must be used daily for storage and disinfection.

WARNING: DO NOT MIX OR ALTERNATE THE DISINFECTION AND STORAGE SYSTEM FLEXSOL® SOLUTION SHOULD NOT BE USED WITH HEAT.

Hygiene: Before handling the lenses, hands must be washed, rinsed thoroughly and dried with a lint-free towel. Cosmetics, lotions, soaps, oil and hand creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the spray has settled.

Fluorescein: Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with LENSRINS® or BOIL n SOAK® and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein.

ADVERSE REACTIONS: Serious corneal damage may result from wearing lenses which may have soaked in hard contact lens solutions. Eye irritation may occur within a short time after putting on a hypotonic lens. Removal of the lens will relieve the irritation.

Very rarely a lens may adhere to an eye as a result of a patient sleeping with the lens on, as a result of wearing a hypotonic lens. If a lens adheres for any reason, the patient may be instructed to apply a few drops of LENSRINS® or BOIL n SOAK® Solution (if using a thermal disinfection regimen) or ADAPETTES® Cleaning and Rewetting Solution (sterile, isotonic buffered solution containing Adsorbobase and preserved with thimerosal 0.004% and edetate disodium 0.1%) (if using a chemical disinfection regimen), and wait until the lens moves freely before removing it.

Clinical studies indicate that corneal edema as manifested by symptoms such as rainbows or halos around light or visual blurring may occur if lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. If symptoms do not subside promptly, professional consultation should be obtained.

Excessive tearing, unusual eye secretions and photophobia are not normal. If these symptoms occur, the patient should be examined to determine their cause.

DOSAGE AND ADMINISTRATION: Fitting: Conventional methods of fitting contact lenses do not apply to AOTHIN™ Soft Contact Lenses. For a detailed description of the fitting technique, refer to the Fitting Guide for AOTHIN™ (tetrafilcon A) Soft Contact Lenses, copies of which are available from: American Optical Corp., Vision Care Products, Southbridge, MA 01550.

Wearing Schedule: There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient.

Day	Wear Time *(Hours)*	Rest Period *(Hours)*	Wear Time *(Hours)*
1	4	2	4
2	4	2	4
3	5	2	5
4	6	2	5
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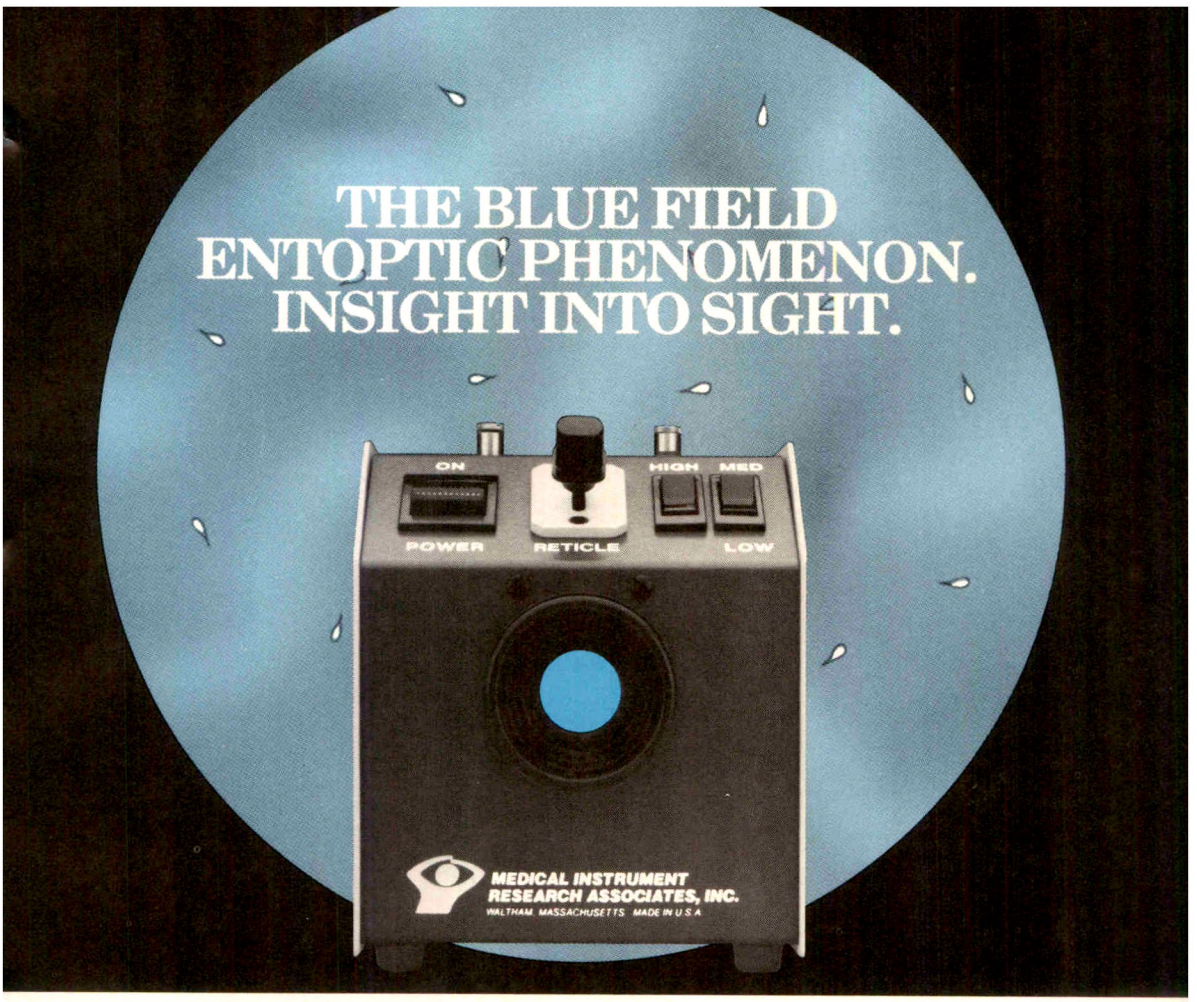

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[1] Sinclar, S., Riva, E., Loebl, M.: Blue field entoptic phenomenon in cataract patients. Archives of Ophthalmology 97: 1092, 1979.

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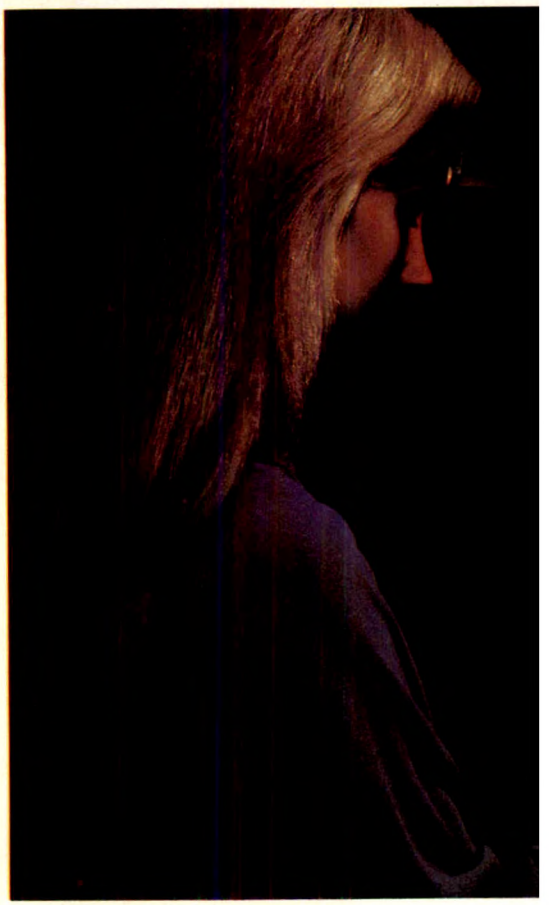

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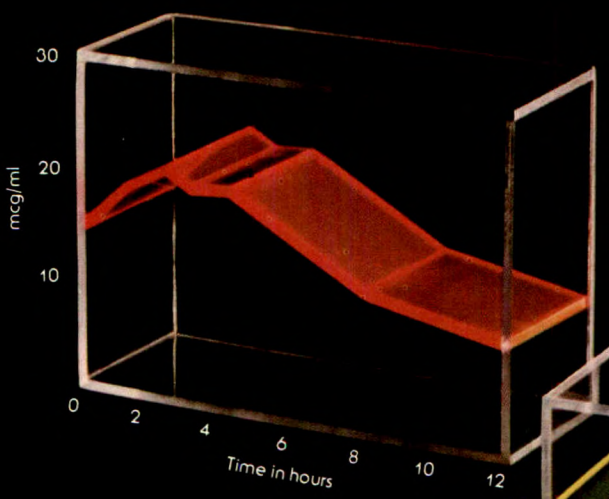

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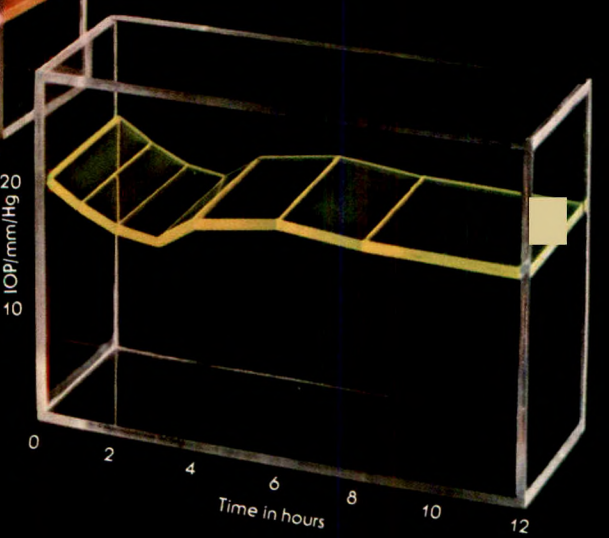

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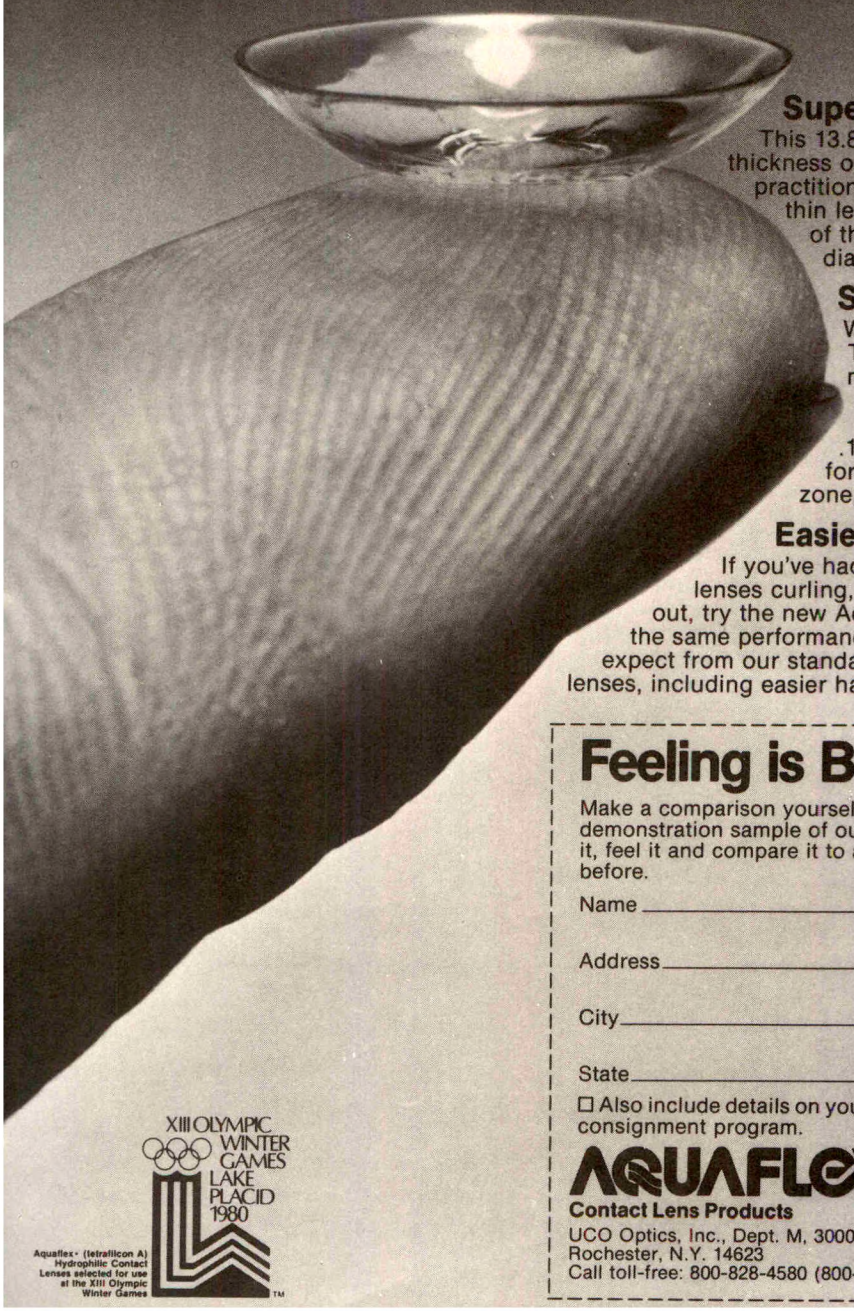

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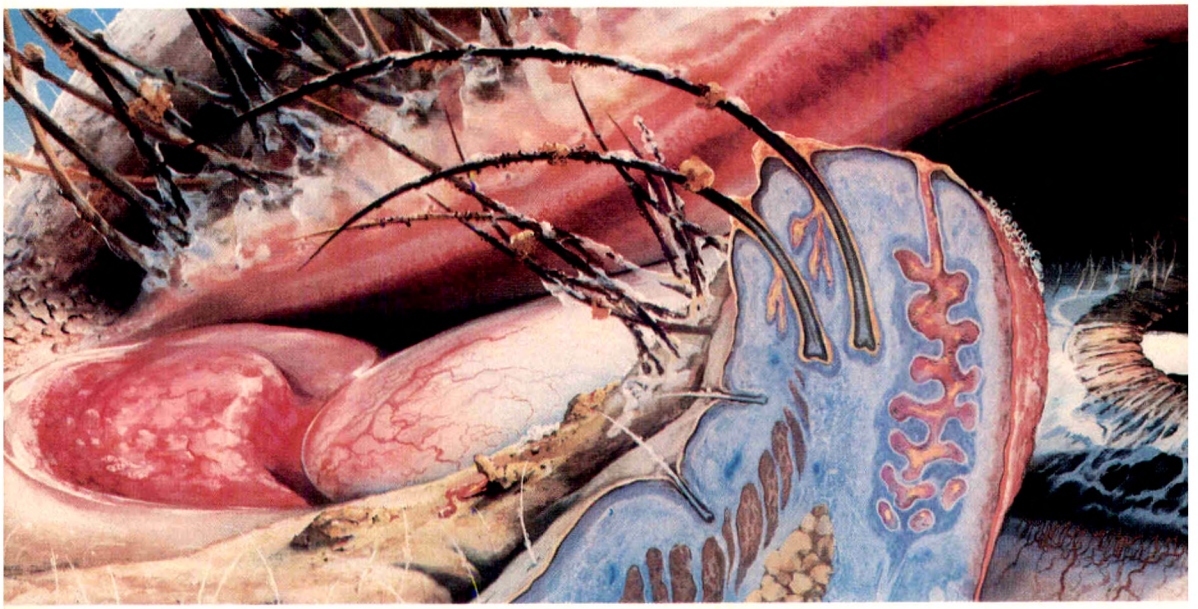

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AMERICAN JOURNAL OF OPHTHALMOLOGY™

VOLUME 89 NUMBER 5 MAY, 1980

FURTHER OBSERVATIONS ON A 13qXp TRANSLOCATION ASSOCIATED WITH RETINOBLASTOMA

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Tucson, Arizona

In the last few years much interest has been centered on the group of patients genetically predisposed to retinoblastoma. These tumors occur either as a dominant mendelian form of transmission or are associated with deletion of the long arm of chromosome 13. Both of these genetically predisposed forms have been useful in the development of hypotheses regarding the origin of malignancy,[1,2] especially in comparison to the sporadic form of the disease. In the case of retinoblastoma associated with abnormalities of chromosome 13, 22 cases have been reported.[3-22] Of these, 14 were studied by banding techniques and band 13q14 was involved in each case.[10-13, 15-22] Most of these involved a deletion of all or part of this band, but in one case reported by Cross and associates[18] a balanced translocation between chromosome 13 and the X chromosome was involved. In the initial report the observations were interpreted as a translocation of the long arm of 13 on to the short arm of one X chromosome with a breakpoint at 13q14 without the loss of X chromosome material. Barr body measurements and autoradiographic determination of the late labeling X chromosome in a few peripheral leukocytes indicated the normal X chromosome was late labeling. This led to the interpretation of the loss of a portion of band 13q14

From the Department of Cytogenetics, Institute of Medical Research, Camden, New Jersey (Drs. Nichols and Miller, Mr. Sobel, and Ms. Hoffman); the School of Medicine, University of California, Los Angeles, California (Dr. Sparkes); the Harbor-UCLA Medical Center, Torrance, California (Dr. Mohandas); and the University of Arizona College of Medicine, Tuscon, Arizona (Ms. Veomett and Dr. Davis).
This study was supported by grant NO3-PO1-AG 00378 and contract NO1-AG4-2865 (Dr. Nichols) from the National Institutes of Health. Dr. Nichols is the S. Emlen Stokes Professor of Genetics at the Institute for Medical Research.
Reprint requests to Warren W. Nichols, M.D., Department of Cytogenetics, Institute for Medical Research, Copewood St., Camden, NJ 08103.

as the factor producing the retinoblastoma. Riccardi and associates[20,23] commented on the original report[18] and suggested the published figures of the derivative X chromosomes were compatible with a mosaic chromosome pattern with a cell line with a breakpoint at 13q12, and another line that was partially deleted with the loss of all of band 13q21 and approximately the distal half to two thirds of band 13q14. This secondary interstitial deletion after the primary reciprocal translocation would produce one line monosomic for the distal portion of 13q14 and produce the retinoblastoma. Riccardi and associates[20] also stated that although the findings were compatible with an inactivation via heterochromatinization of the derivative X chromosome producing a functional monosomy for 13q14, this was unlikely on the basis of the original observations by Cross and associates;[18] that is, the late replicating normal X chromosome in peripheral lymphocytes.

We report further observations made in two additional studies as well as the original study done on a fibroblast cell line derived from this patient.

Material and methods

Additional banding studies were done by a modification of the Giemsa-trypsin method of Seabright[24] and the quinacrine fluorescence technique.[25] Late labeling studies of the X chromosome were performed with tritiated thymidine and autoradiography,[26] reverse banding with bromodeoxyuridine[27] and bromodeoxyuridine acridine orange fluorescence.[26] Studies to differentiate between active and inactive X chromosomes were also made by making somatic cell hybrids between these fibroblasts and rodent cells lacking the hypoxanthine-guanine-phosphoribosyltransferase enzyme, and selecting with hypoxanthine-aminopterin-thymidine.[28,29] Because human chromosomes are lost from the hybrids under the conditions of the experiment and only cells that have hypoxanthine guanine phosphoribosyltransferase can survive in hypoxanthine-aminopterin-thymidine medium, clones can be selected that have retained an active human X chromosome. Which X chromosome is retained under these circumstances can be determined cytogenetically and the genetic activity can be confirmed by the expression of human glucose-6-phosphate dehydrogenase which is also coded on the X chromosome.

Results

In contrast to the earlier studies, all of the banded karyotypes made from skin fibroblasts by both techniques in both additional laboratories and the original laboratory of this patient show that the breakpoints in chromosome 13 were at the junction of band q12 and band q13, with band q13 being visible in the segment translocated to the short arm of the X chromosome (Figs. 1 and 2). These examinations were made on 101 cells. This breakpoint was confirmed when the original material prepared from blood cells was reviewed by two of us (I.V. and J.R.D.). Therefore, it appears that the original breakpoint was determined on the basis of a misinterpretation of the densitometric studies. No evidence was found in the material for mosaicism. Late labeling studies on fibroblasts by the three techniques showed the abnormal X chromosome to be late labeling in every one of the 104 cells examined (Figs. 3-5).

In the studies of somatic cell hybrids derived from the fusion of fibroblasts with rodent cells followed by selection with hypoxanthine-aminopterin-thymidine medium, eight independent hybrid lines were obtained. Seven of these hybrid lines retained the normal X chro-

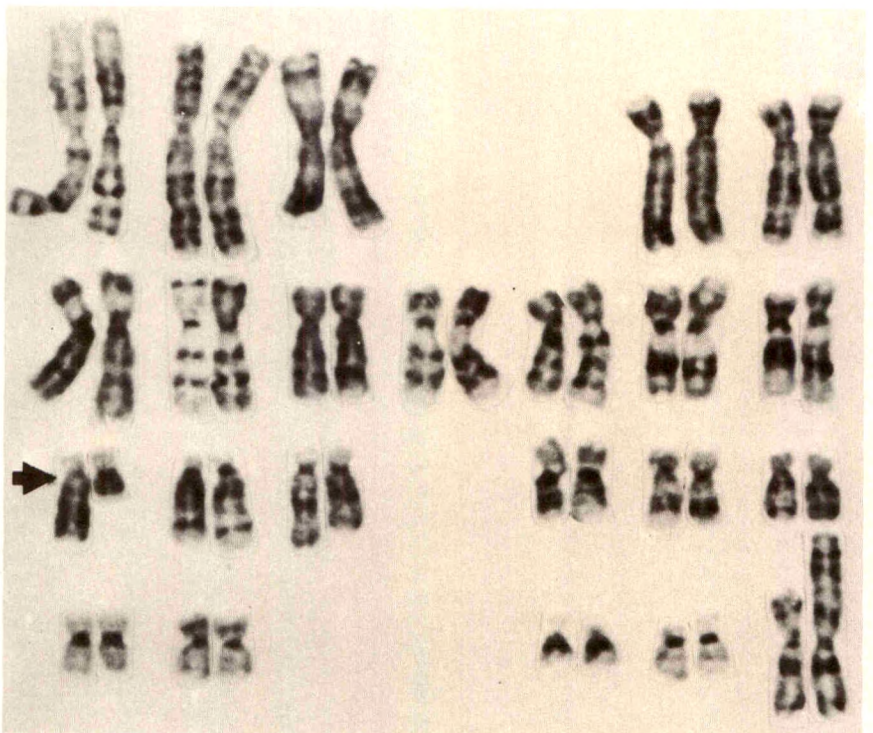

Fig. 1 (Nichols and associates). Giemsa banded karyotype showing 13; X translocation with band 13q13 included in the segment on the X chromosome (arrow).

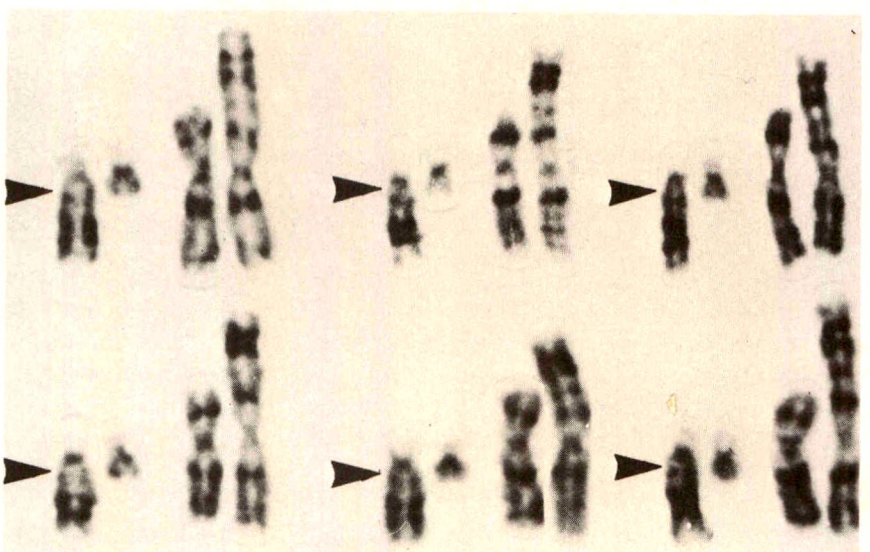

Fig. 2 (Nichols and associates). Partial karyotypes from seven cells showing the above translocation with breakpoint in band 13q12 (arrows).

Fig. 3 (Nichols and asso ciates). Banded karyotyp above and late labeling wit tritiated thymidine belo showing heavy labeling of th translocated X chromosome

mosome and coordinately expressed human glucose-6-phosphate dehydrogenase. Four of these were then selected in 8-azaguanine and lost the normal X chromosome and the expression of human glucose-6-phosphate dehydrogenase. The eighth hybrid line retained the X-13 derivative chromosome and expressed human glucose-6-phosphate dehydrogenase and esterase D, the latter being coded on chromosome 13. When these were then selected with 8-azaguanine this X-13 translocation chromosome was lost, as was the expression of human glucose-6-phosphate dehydrogenase and esterase D.

Discussion

We found in both the review of the original blood cell preparations and the additional fibroblast analyses that the breakpoint of chromosome 13 is clearly at

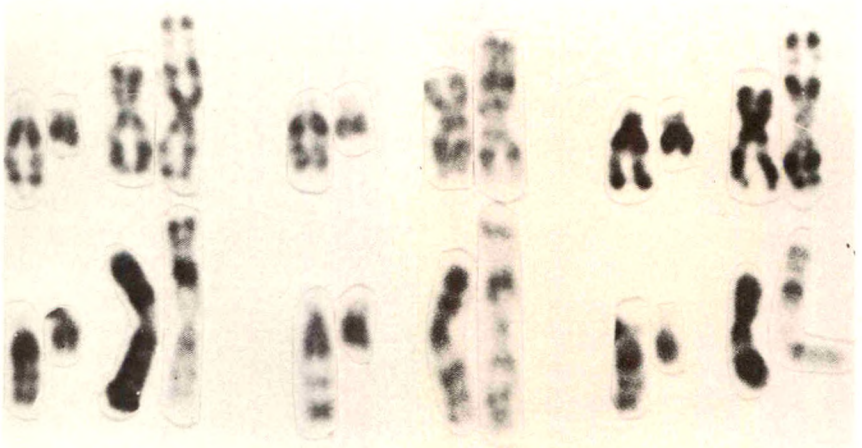

Fig. 4 (Nichols and associates). Partial karyotypes from bromodeoxyuridine reverse banding showing late labeling of translocated X chromosome.

the junction of band q12 and q13, with band q13 being included in the translocation to the short arm of the X chromosome. It follows, therefore, that band 13q14 is also in the segment translocated to the X chromosome. Because most of the evidence indicates that the chromosomal abnormality asociated with retinoblastoma involves a partial or complete deletion of band 13q14, the most likely

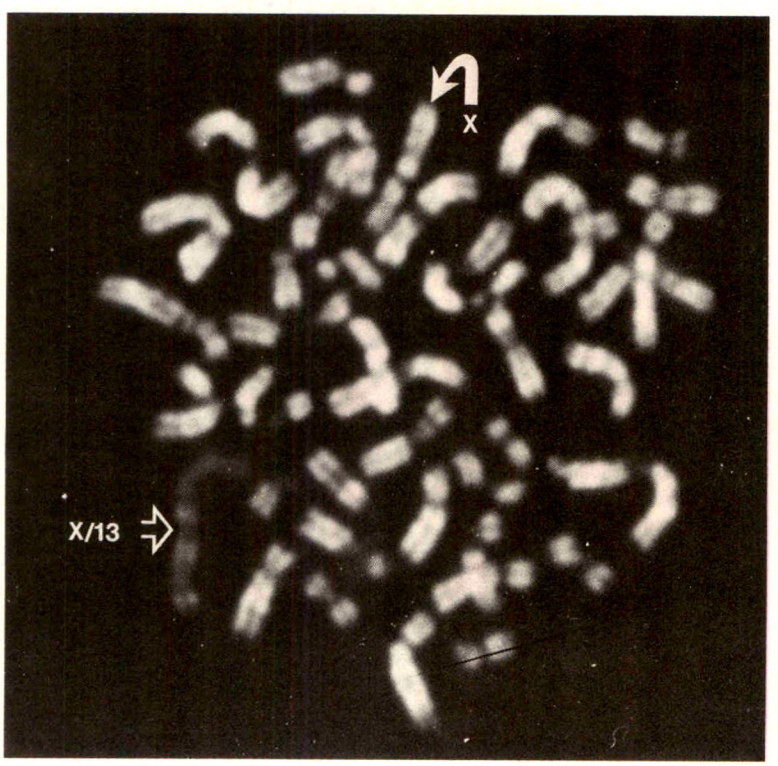

Fig. 5 (Nichols and associates). Late labeling with bromodeoxyuridine acridine orange fluorescence showing late labeling of translocated chromosome.

explanations for the present case are either a functional monosomy for band q14 because of heterochromatinization and inactivation of the derivative X chromosome via lyonization, or a mosaicism with an interstitial deletion in some cells, as suggested by Riccardi and associates.[20,23] Predominance of cells with the derivative X chromosome inactivated and the lack of evidence of mosaicism for an interstitial deletion make the first possibility appear more likely. It is clear that the translocated X chromosome is the one usually showing late labeling. Also, the translocated portion of chromosome 13 is lighter than its normal homologue in the reverse banding preparations (seen best in band 13q22), and thus is an indication of probable spreading of the heterochromatic inactivation to the translocated segment of chromosome 13. However, because chromosome 13 normally is late labeling, the differences between the normal 13 and the translocated 13 are not dramatic, and it is not possible to establish definitively the spread of inactivation on a cytogenetic basis alone. Demonstration of a quantitative reduction in the amount of esterase D produced in these cells compared to normal would directly illustrate this point.

The difference in the inactivation findings in the leukocyte culture may be because of tissue differences resulting from random X chromosome inactivation in precursor cells or from the small number of cells that were suitable for examination in the original study. The presence of an active X-13 chromosome in one hybrid cell line supports random inactivation of the X chromosomes in this patient and points to the existence of a small population of cells even in the fibroblasts in which the normal X chromosome is inactivated, although late replication studies done directly on the fibroblasts failed to show the presence of these cells. Genetic inactivation of the 13q14 band in the derivative X chromosome is therefore hypothesized as the predisposing factor in this case of retinoblastoma.

Summary

In a patient with a 13qXp translocation and retinoblastoma the band associated with retinoblastoma (13q14) was clearly translocated intact to the X chromosome rather than being the breakpoint of the translocation. Genetic inactivation of the derivative X chromosome shown by late labeling and cell hybridization techniques in the predominance of cells indicated a functional monosomy for this segment as the most likely predisposing factor in producing retinoblastoma.

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IMMUNE COMPLEXES AND CARCINOEMBRYONIC ANTIGEN LEVELS IN METASTATIC CHOROIDAL TUMORS

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Approximately 50% of metastatic choroidal tumors are diagnosed before discovery of the primary neoplasm.[1] Laboratory tests may be useful in the differentiation of metastatic choroidal tumors from primary choroidal tumors. In many human cancers, immune complexes, consisting of antigens and antibodies, have been shown in patients' sera.[2] In some, but not all malignancies, increased levels of immune complexes are observed more often in patients with widespread vs localized disease.[3]

We studied immune complex and carcinoembryonic antigen levels in patients with metastatic choroidal tumors. When both assays are used, greater than 90% of patients with metastatic choroidal melanoma tumors may be identified.

SUBJECTS AND METHODS

Patients were examined here. All had a standard ocular oncology examination for their choroidal tumor including a general history and physical examination, Goldmann perimetry, indirect ophthalmoscopy, fundus photography, fluorescein angiography, and ultrasonography using both quantitative echography and B-scan ultrasound examination. Diagnosis was based on the clinical evaluation in the Ocular Oncology Unit. Eleven patients with systemic tumors metastatic to the choroid and one patient with a choroidal melanoma with systemic metastases were studied. Metastatic disease was documented in all patients. At the time of ocular examination, six patients with metastatic choroidal tumors had concomitant nonocular metastases; four patients had choroidal metastases as the initial signs of widespread disease (Table 1).

All laboratory studies were performed in a masked manner. Immune complex levels were measured by a modified Raji cell radioimmunoassay; an immune complex level greater than 25 μg/ml (aggregated human IgG equivalent) was considered abnormal (>2 SD above the mean).[4,5] Twenty-nine of 31 (94%) of the normal subjects simultaneously tested had immune complex levels less than this. Carcinoembryonic antigen determinations were performed using

TABLE 1

OCULAR AND SYSTEMIC STATUS OF 11 PATIENTS WITH METASTATIC CHOROIDAL TUMORS

Patient No.	Ocular Involvement	Systemic Metastases*
1	Unilateral, multiple tumors	+
2	Unilateral, single tumor	−
3	Unilateral, single tumor	−
4	Bilateral, multiple tumors	+
5	Unilateral, multiple tumors	−
6	Unilateral, multiple tumors	+
7	Bilateral, multiple tumors	+
8	Unilateral, multiple tumors	+
9	Bilateral, multiple tumors	+
10	Unilateral, multiple tumors	−
11	Bilateral, multiple tumors	+

*+ indicates positive; −, negative.

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the carcinoembryonic antigen-RAI kit (Hoffman-LaRoche); a carcinoembryonic antigen value of greater than 10 ng/ml was considered abnormal.[6,7] Statistical evaluation was performed by using the Chi-square test and Mann-Whitney test.

Results

Nine of 11 patients with metastatic choroidal tumors had increased immune complex levels; increases were observed in three of four patients with isolated choroidal metastases and five of seven patients with widespread disease (Table 2). Four patients with metastatic choroidal tumors had carcinoembryonic antigen levels greater than 10 ng/ml; these included three of six patients with widespread metastases and one of four patients with isolated choroidal lesions.

All patients with choroidal melanoma had carcinoembryonic antigen levels greater than 10 ng/ml. Ten of 43 choroidal melanoma patients had increased immune complex levels (>25 μg/ml aggregated human IgG equivalent); one patient had developed metastases; six patients have concomitant disease (rheumatoid arthritis, dermatomyositis, and Sjögren's disease); three patients have increased levels without the clinically detectable metastatic disease or other diseases associated with immune complex increases.[8-11] The difference in the incidence of abnormal immune complex or carcinoembryonic antigen levels in patients with metastatic choroidal tumors and those with choroidal melanomas or normal controls was statistically significant ($P < .005$).

Discussion

Ten of 11 patients (91%) with metastatic choroidal tumors had an increase of either immune complex or carcinoembryonic antigen levels. As Michaelson, Felberg, and Shields[6,7] have described, approximately 50% of the patients with metastatic lesions have abnormal carcinoembryonic antigen values (>10 ng/ml); in the current study only four of ten patients with metastatic choroidal tumors had carcinoembryonic antigen levels greater than 10 ng/ml. Fewer

TABLE 2

IMMUNE COMPLEX AND CARCINOEMBRYONIC ANTIGEN LEVELS OF PATIENTS WITH METASTATIC CHOROIDAL TUMORS*

Patient No.		Raji Radioimmunoassay, μg (Aggregated Human IgG Equivalent/ml)	Carcinoembryonic Antigen (ng/ml)
		Metastatic Choroidal Breast Carcinoma	
1		56 (+)	2.5 (−)
2		5 (−)	140 (+)
3		40 (+)	4.2 (−)
4		28 (+)	100 (+)
5		88 (+)	3.5 (−)
6		18 (−)	8.1 (−)
7		85 (+)	
		Miscellaneous Choroidal Metastases	
8	Lung	56 (+)	20 (+)
9	Thyroid	103 (+)	3990 (+)
10	Stomach	25 μg (±)	6.6 (−)
11	Pancreas	98 (+)	6.2 (−)
		Choroidal Melanoma With Widespread Metatases	
12		530 (+)	6.2 (−)

*+ indicates positive; −, negative.

patients with isolated choroidal metastases had increased carcinoembryonic antigen levels than did patients with widespread disease (one of four vs three of six); however, the number of patients studied is too few for significant conclusions to be drawn. In some neoplasms carcinoembryonic antigen levels correlate with tumor burden.[12] This may explain the relatively low sensitivity of the carcinoembryonic antigen assay in the diagnosis of metastatic choroidal tumors because many patients have ocular lesions as the only manifestation of widespread disease.[1]

Increases in immune complex levels were detected in nine of 11 (82%) patients with metastatic choroidal tumors. In some malignancies, immune complex levels are an early and sensitive indicator of disease status and prognosis; however, on other tumors they are not.[3] Immune complex determinations may be a more sensitive means of detecting metastatic choroidal tumors than the carcinoembryonic antigen assay; however, further data are necessary to determine this.

In this study the specificity of the Raji assay was less than the carcinoembryonic antigen test in the diagnosis of metastatic choroidal disease. We observed no carcinoembryonic antigen level greater than 10 ng/ml in primary choroidal melanoma patients; however, ten of 43 melanoma patients had immune complex increases. Immune complexes have been detected in a number of diseases including rheumatologic, hematologic, and neoplastic processes.[8-11] In patients with choroidal tumors with no other systemic diseases, an increase of either immune complex or carcinoembryonic antigen levels may suggest the possibility of a metastatic lesion. Although immune complex increases are often present in patients with metastases, they are not specific for this diagnosis and may be increased in many other conditions; they should not be used as the sole diagnostic criteria for metastatic choroidal tumors.

In one patient with a choroidal melanoma who developed metastatic disease, an increase in immune complex levels was detected early in the metastatic disease process. In systemic melanoma, the levels of immune complexes have correlated with both disease status and prognosis.[13] Many patients with choroidal melanomas are treated with modalities other than enucleation.[14] As more patients are conservatively managed, better prognostic guides must be established; possibly immune complex determinations will increase our ability to predict accurately the prognosis in choroidal melanoma.

Summary

We studied 11 patients with metastatic choroidal tumors and one patient with a metastatic choroidal melanoma by using the Raji cell radioimmunoassay to detect immune complexes, and the carcinoembryonic assay. Ten (91%) patients with choroidal metastases had an increase of either immune complex levels or carcinoembryonic antigen results.

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Ophthalmic miniature

To look at a star by glances—to view it in a sidelong way, by turning toward it the exterior portions of the retina (more susceptible of feeble impressions of light than the interior), is to behold the star distinctly—is to have the best appreciation of its lustre—a lustre which grows dim just in proportion as we turn our vision fully upon it. A greater number of rays actually fall upon the eye in the latter case, but, in the former, there is the more refined capacity for comprehension. By undue profundity we perplex and enfeeble thought; and it is possible to make even Venus herself vanish from the firmament by a scrutiny too sustained, too concentrated, or too direct.

Edgar Allan Poe
Murders In The Rue Morgue

MELANOCYTOMA OF THE CILIARY BODY AND IRIS

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The melanocytoma (magnacellular nevus) is a deeply pigmented intraocular tumor that is usually located on the optic nerve head. It is recognized as a variant of a benign nevus with distinctive clinical and pathologic features.[1-3] Despite its benign cytology, the melanocytoma of the optic disk may undergo slow growth[4] and may produce visual field defects and pupillary abnormalities.[5] In rare instances a melanocytoma may occur in the choroid,[6] iris,[7] and ciliary body.[8,9] In some cases these extrapapillary melanocytomas may show extrascleral involvement or signs of enlargement[10] that make the clinical differentiation from malignant melanoma extremely difficult. We describe herein a patient with a melanocytoma of the ciliary body that involved the iris and encroached upon the lens. The eye was enucleated; the clinical diagnosis was malignant melanoma.

CASE REPORT

A 29-year-old woman consulted her ophthalmologist in December 1978 because of a "spot" on the iris of her left eye. The patient reported progressive enlargement of the iris lesion for about three to four months. Her last ocular examination two years earlier, which included slit-lamp biomicroscopy, had shown no evidence of the iris tumor. The patient was referred to one of us (J.A.S.) for diagnosis and management.

Our examination showed an uncorrected visual acuity of 6/6 (20/20) in both eyes and intraocular pressures of 13 mm Hg in both eyes by applanation tonometry. Slit-lamp examination showed a well-delineated pigmented mass in the temporal portion of the left iris (Fig. 1). The mass appeared to be pushing the iris stroma aside, indicating that it had grown forward from the ciliary body. Examination through the dilated pupil showed the bulk of the tumor to be in the ciliary body. The tumor was touching the inferotemporal equator of the lens, which was slightly subluxated. The mass extended from the 2 to 5 o'clock meridians of the ciliary body and extended about 1.0 mm posterior to the ora serrata. Transillumination showed a round shadow approximately 7 mm in diameter involving the inferotemporal portion of the ciliary body.

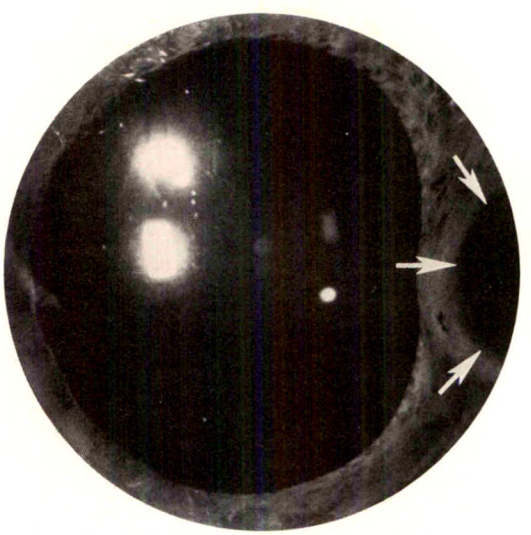

Fig. 1 (Shields and associates). Anterior segment showing deeply pigmented mass replacing the iris on temporal side (arrows).

From the Pathology Department and the Oncology Unit, Wills Eye Hospital, Philadelphia, Pennsylvania (Drs. Shields, Augsburger, Bernardino, and Eller); and the Department of Ophthalmology, Guthrie Clinic, Sayre, Pennsylvania (Dr. Kulczycki). This study was supported in part by the Retina Research and Development Foundation, Philadelphia, Pennsylvania, and the Pennsylvania Lions Sight Conservation and the Eye Research Foundation, Inc.

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Ocular B-scan ultrasonography showed a discrete dome-shaped mass originating from the ciliary body. The A-scan showed internal echoes of moderately low intensity compatible with malignant melanoma.[11]

An incisional radioactive phosphorus (^{32}P) uptake test [12,13] performed 48 hours after administration of the isotope showed an uptake of 108% as compared to control sites. Our clinical diagnosis was malignant melanoma of the ciliary body. Because the tumor was too large to manage successfully by iridocyclectomy, the eye was enucleated.

Results

Gross examination showed a normal-sized left eye with a pigmented tumor involving the iris inferotemporally. Transillumination showed a shadow extending posteriorly from the corneoscleral limbus and measuring about 7 mm in diameter.

The sectioned globe showed a deeply pigmented ciliary body mass that measured about 8 mm in diameter through the base and 6 mm in greatest elevation. The tumor was in apposition to the lens equator and had produced a slight subluxation of the lens. The tumor extended through the iris root and was present in the anterior chamber.

Low-power microscopy showed a deeply pigmented mass originating from the ciliary body (Fig. 2). The tumor replaced the peripheral iris and trabecular meshwork in the involved quadrant. The tumor was composed of plump cells with such closely packed pigment granules in the cytoplasm that the nuclei stood out as lighter areas. Cystic spaces within the tumor contained pigment laden macrophages and free tumor cells. Bleached preparations showed round to oval cells with distinct round nuclei. Unusually prominent nucleoli and mitotic figures were not present (Fig. 3). The cells were identical to those characteristic of a melanocytoma.[1,2]

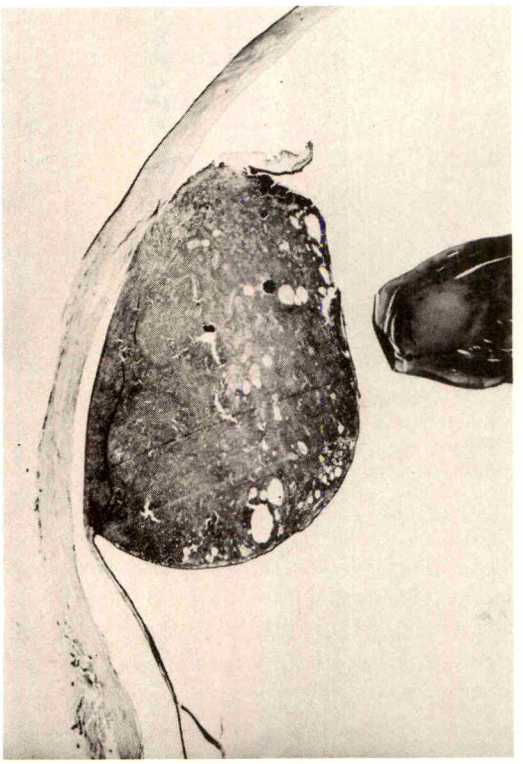

Fig. 2 (Shields and associates). Low-power photomicrograph of temporal anterior chamber angle region. Note replacement of the peripheral iris stroma and trabecular meshwork by the deeply pigmented tumor (hematoxylin and eosin, ×20).

Discussion

The melanocytoma of the optic papilla has distinctive clinical features that have been well described.[1-5] Cogan proposed the term magnacellular nevus, which may be a more appropriate designation.[14] When a tumor composed of similar cells occurs in an extrapapillary location, it may be impossible to differentiate it clinically from malignant melanoma.

There were several reasons why the diagnosis of malignant melanoma was strongly suspected in this case. These included the size and the dark brown color of the lesion, the patient's history of growth of the lesion, the normal results of the ophthalmic examination two years before detection of the tumor, and the results of the ancillary diagnostic studies.

With regard to the size of the lesion, typical benign melanocytic tumors of the uveal tract (nevi) rarely attain a thickness

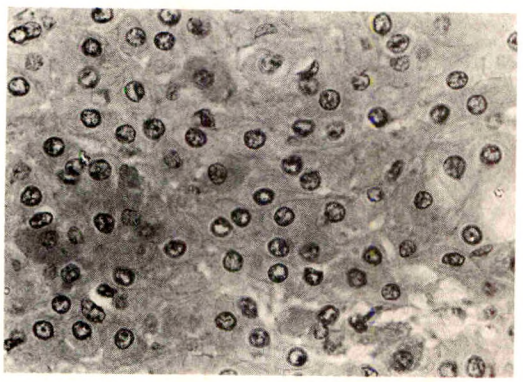

Fig. 3 (Shields and associates). Photomicrograph of bleached specimen showing characteristic plump cells with benign cytologic features (bleached preparation, hematoxylin and eosin, ×100).

greater than 2.0 mm.[15] Most histologically documented malignant melanomas are greater than 2 mm in thickness. Because the tumor thickness in our case was 6 mm, we considered it unlikely to be a nevus.

The lesion was dark brown rather than black. Most melanocytomas of the optic disk[1-3] or the iris[7] appear black. Involvement of the iris coupled with the patient's history that the lesion had enlarged indicated that this was a growing lesion. Most benign melanocytic tumors of the uvea are believed to be stationary, nonprogressive lesions that remain dormant throughout the patient's life. However, slow enlargement of some melanocytomas of the optic disk has been shown.[4]

Ultrasonography[11] and the ^{32}P uptake test[12] have been reported to be highly reliable in differentiating malignant melanomas of the ciliary body from many benign lesions. In this case, ultrasonography was consistent with the diagnosis of malignant melanoma. This is not surprising because the closely packed cells of a melanocytoma would be expected to produce echographic features similar to those of closely packed cells present in most uveal melanomas. Despite the benign cytology of this lesion, the incisional ^{32}P uptake test gave a positive result. However, in our experience most malignant melanomas of the ciliary body of a size comparable to that of our patient's tumor give a ^{32}P uptake test result much higher than 100%.[12] We believe that a minimally positive ^{32}P uptake test should possibly be viewed with suspicion if it occurs with a tumor of this size.

Thorough clinical examination of our patient's tumor, including the use of currently available ancillary tests, failed to show its benign nature before enucleation. The problem of erroneous diagnosis of malignant melanoma of the uvea may never be entirely eliminated.

Summary

A 29-year-old woman had a pigmented ciliary body mass that extended through the iris into the anterior chamber. On the basis of clinical findings and ancillary diagnostic studies, the clinical diagnosis was malignant melanoma of the ciliary body. The enucleated eye showed the tumor to be composed of cells identical to those of a melanocytoma of the optic disk.

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Ophthalmic miniature

. . . it was with my wounded eye that I was seeing this gang of brigands. You see for yourself by this pucker and scar how the thin blade passed between socket and ball, but it was only at that moment, when I was dragged from the coach, that I understood that my sight was not gone forever. The creature's intention, doubtless, was to drive it through into my brain, and indeed he loosened some portion of the inner bone of my head, so that I afterwards had more trouble from that wound than from any one of the seventeen which I have received.

Sir Arthur Conan Doyle
The Exploits of
Brigadier Gerard
New York, Appleton, 1896

ORBITAL CARCINOID TUMOR METASTATIC FROM THE COLON

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Metastatic neoplasms cause from 3 to 9% of orbital tumors.[1] Although 153 malignant tumors metastatic to the orbit from distant sites have been described in reports from several countries,[2-10] only one case of a malignant carcinoid orbital tumor has been reported.[9,10] Carcinoid tumors are a heterogeneous group of neoplasms of the enterochromaffin cells of the gastrointestinal tract and of similar cells in the bronchial tree, biliary tract, and pancreatic duct that are also derived from the embryonic gut. Bronchial carcinoid tumors have previously been reported to metastasize to the eye,[11,12] but intestinal carcinoids metastatic to the eye and adnexa are extremely rare.[9] Font and Ferry[10] have reported one case of an ileal carcinoid tumor metastatic to the orbit, but, to the best of our knowledge, we report the first case of a documented metastatic carcinoid tumor whose primary site was the colon.

CASE REPORT

A 58-year-old woman was referred here for evaluation of left-sided exophthalmos of one week's duration. She had been in good health until early June 1979, when she was hospitalized elsewhere for the sudden onset of intermittent abdominal cramps associated with nausea, vomiting, and diarrhea. Findings on physical examination were normal except for abdominal distention, diminished bowel sounds, and diffuse abdominal tenderness, symptoms that were consistent with bowel obstruction. Laboratory tests showed a hematocrit of 39% and hemoglobin of 12.7 g/100 ml. Normal laboratory tests included routine serum chemistries, bilirubin, alkaline phosphatase, electrolytes, and urinalysis. A chest roentgenogram was normal, but a barium enema performed on the second hospital day disclosed an annular constricting lesion of the proximal colon. On June 25, 1979, a bulky tumor involving the hepatic flexure and proximal 35 cm of colon was resected (Fig. 1). Palpable mesenteric nodes extending from the lesion to the para-aortic area were present.

Postoperatively, the patient was well until July 6, 1979, when left-sided exophthalmos, chemosis, and diplopia suddenly occurred. The patient was referred to the Mayo Clinic on July 11, 1979, and findings on a general examination, other than a well-healing abdominal scar, were unremarkable. Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/7.5 (20/25). Near visual acuity was 4/6 (14/21) in both eyes. External examination of the left eye showed a proptosis of 7 mm, as measured by a Hertel exophthalmometer. Moderate conjunctival chemosis and blepharoptosis of the left upper eyelid (2 mm) were noted. All of the extraocular muscles of the left eye were involved, with particular weakness of the superior rectus and inferior oblique muscles. Results of forced duction tests were normal. Pupillomotor function was preserved, and there was no afferent pupillary defect. No mass was palpable in the anterior orbit. Intraocular pressure was 14 mm Hg bilaterally, and findings on ophthalmoscopy were normal in each eye.

Normal laboratory tests included a routine com-

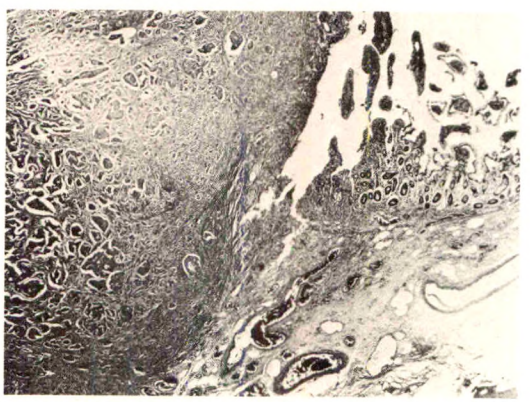

Fig. 1 (Rush, Waller, and Campbell). Uniform small cells with hyperchromatic nuclei are arrayed in well-defined nests (classic pattern) and in interanastomotic strands (trabecular pattern). Muscle coat of colon shows hypertrophy. Normal colon is at right (hematoxylin and eosin, ×16).

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plete blood cell count, serum chemistry group, and urinalysis. A 24-hour collection of 5-hydroxyindoleacetic acid showed a strikingly increased level of 138.1 mg (a normal value is less than 10 mg/24 hours). A chest roentgenogram was normal. Roentgenograms of the orbit showed soft tissue swelling in the left orbit but no bone destruction (Fig. 2). Computed tomography scans of the head and orbit showed a large mass in the left orbit, extending from the apex along the superior and inferior rectus muscles and displacing the optic nerve anteromedially (Fig. 3). A liver scan was nondiagnostic.

On July 26, 1979, as the result of an anterolateral orbitotomy of the left orbit and biopsy of the lesion, a diagnosis of metastatic carcinoid tumor was made (Fig. 4). The left orbit was irradiated with 3,500 rads of radioactive cobalt (^{60}Co), and the ocular motility and exophthalmos of the left eye improved. By Aug. 28, 1979, the chemosis had resolved.

Discussion

The carcinoid tumor, derived from tissue whose embryonic precursor is the primitive endoderm, occurs in organs differentiated from the embryonic gut. The cells of origin are the chromaffin cells lining the gastrointestinal crypts of Lieberkühn and similar cells of the bronchial tree. The term carcinoid refers to the fact that these cells, whose biologic behavior is comparatively benign, are histologically similar to carcinoma cells. Decades after the term was coined, the potentially malignant activity of this tumor became known.

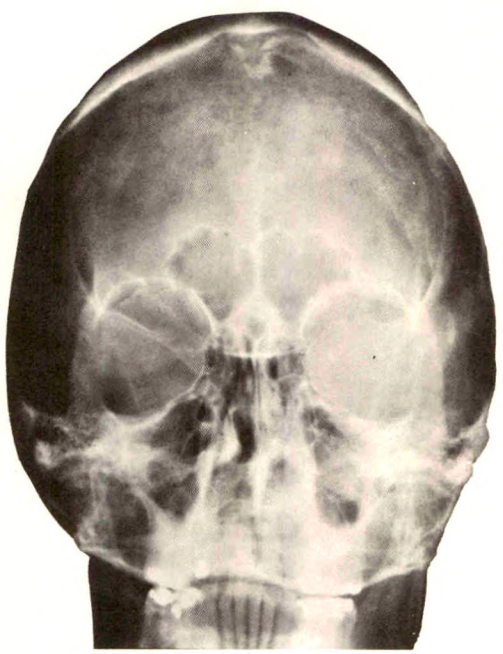

Fig. 2 (Rush, Waller, and Campbell). Posteroanterior roentgenogram of skull, showing soft tissue mass in left orbit and no bone destruction.

The prevalence of gastrointestinal carcinoid tumors is 0.65 to 1.1% of autopsy series[13,14]; these tumors occur throughout the gastrointestinal tract from the stomach to the rectum, sparing only the esophagus. The frequency of carcinoids of the small intestine increases exponentially from the duodenum to the ileum, and carcinoids of the appendix constitute 45% of all gastrointestinal carcinoid tumors.[15] Colonic carcinoids, excluding those originating from the cecum or rectum, occur least often of all intestinal carcinoids, comprising only 28 of the 2,579 tumors in one review series.[15] Despite this low frequency, of all carcinoids, these colonic tumors have the highest rate of local metastases, almost 38%,[15] but the incidence of distant metastases is poorly documented. In one report of 209 patients with carcinoid tumors of the small intestine,[13] metastases developed outside the abdominal cavity in only three patients.

Interestingly, our patient with a carcinoid tumor of the colon manifested clinical symptoms of orbital metastasis within a month after the initial abdominal symptoms. According to Moertel and associates[13] the presence of metastasis seems to be a prerequisite for the clinical diagnosis of carcinoid of the small intestine. Ten times as many patients with intestinal symptoms showed evidence of local metastasis compared with those whose tumor was an incidental finding at autopsy. This may be related to the size of the primary tumor, as these investigators found that only 2% of the lesions less than 1 cm in diameter metastasized,

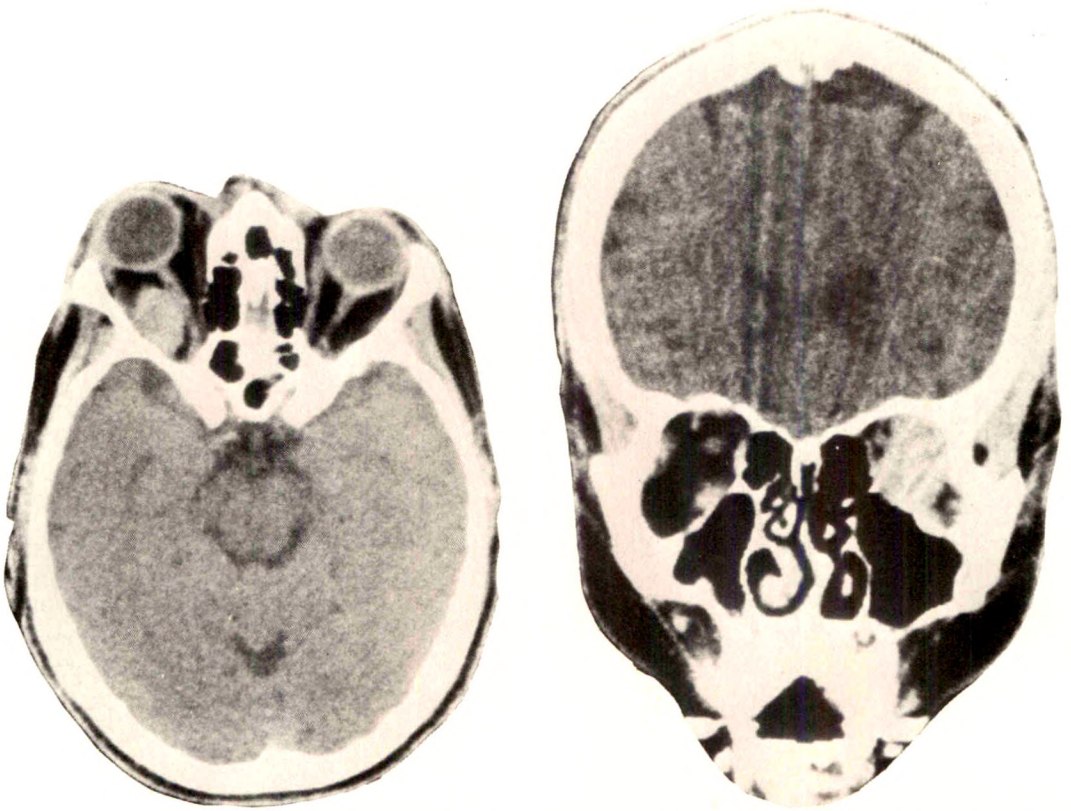

Fig. 3 (Rush, Waller, and Campbell). Computed tomography scans of orbit. Left, Axial thin-section scan without contrast medium, showing intraconal mass in left orbit displacing optic nerve medially. There is no bone expansion or erosion. Right, Coronal thin-section scan through midorbital plane without contrast medium, showing superiorly located mass adjacent to intact orbital roof. Optic nerve and superior rectus muscle are indistinguishable from the lesion.

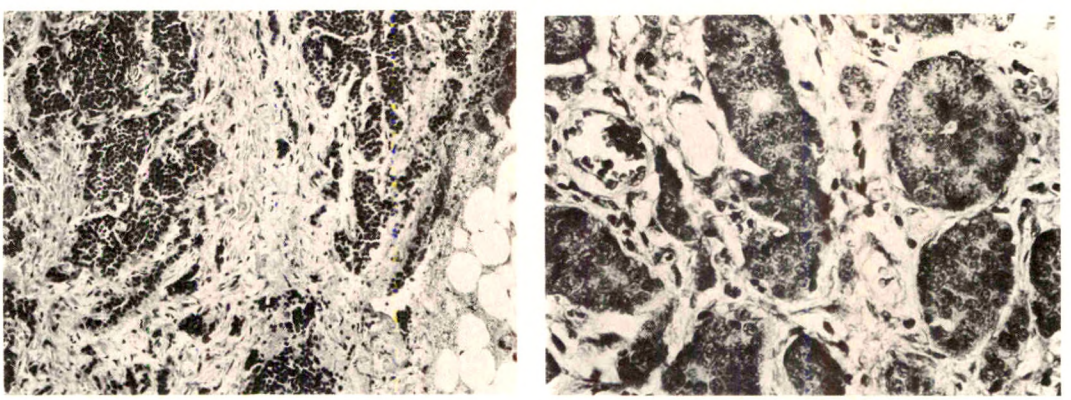

Fig. 4 (Rush, Waller, and Campbell). Left, Histologic appearance of orbital metastasis closely resembles that of primary colonic neoplasm; admixture of both classic and trabecular patterns is present (hematoxylin and eosin, ×160). Right, Argentaffin granules are present in cytoplasm of many of these cells (Masson-Fontana stain, ×400).

whereas 80% of those tumors 2 cm or larger metastasized. Although similar figures have been reported for rectal carcinoid tumors,[16] no data are available for the less common primary carcinoid of the colon. It is nonetheless remarkable that the tumor attained such a large size in our patient before the rapid sequential development of abdominal and orbital symptoms.

Carcinoid tumors are notoriously slow-growing cancers.[15] In our patient, the slow growth of the primary tumor along 35 cm of the bowel wall allowed spreading of tumor cells to the orbit; thus, symptoms of abdominal obstruction and exophthalmos appeared in rapid succession.

An orbital metastatic focus should not deter therapeutic intervention, as the prognosis for patients with carcinoid tumor is favorable. The five-year survival rate is 38% for patients with inoperable nodal or peritoneal spread and 21% for patients with liver metastasis.[13] One patient with orbital metastasis from a carcinoid tumor of the ileum survived nine years after orbital exenteration and 11 years after initial bowel resection.[10] A patient of Rosenbluth, Laval, and Weil,[11] in whom metastatic choroidal involvement developed from a bronchial carcinoid tumor, survived 12 years after enucleation.[12]

The effectiveness of radiation therapy for the treatment of metastatic carcinoid tumor is unproven. Although it was once considered to be radio-insensitive, inoperable abdominal carcinoid tumor has been controlled by total abdominal irradiation in five of ten patients.[17] The results in our patient show that irradiation of orbital carcinoid can help to alleviate proptosis.

Metastatic carcinoid tumors, particularly those that spread to the liver, may also cause the carcinoid syndrome, a symptom complex of intermittent facial flushing, diarrhea, asthma, and endocardial fibrosis of the right side of the heart. These symptoms indicate the presence of a functioning malignant carcinoid tumor, and the diagnosis is confirmed by finding increased levels of 5-hydroxyindoleacetic acid in the urine. This compound is the metabolic end product of serotonin, an endocrine secretion of the enterochromaffin cells of the gastrointestinal tract. Although our patient had a substantially increased 24-hour level of 5-hydroxyindoleacetic acid in the urine (138.1 mg), she did not have typical symptoms of the syndrome, and abdominal exploration as well as liver scan two weeks postoperatively showed no evidence of liver metastasis. Malignant carcinoid tumors spreading from the colon to the liver have produced the carcinoid syndrome, but the syndrome without liver metastases is more commonly seen with tumors spreading from the ileum. Our patient will require close follow-up surveillance for the development of liver metastases or the clinical appearance of the carcinoid syndrome, as the mortality in patients with carcinoid tumor is primarily caused by the effects of serotonin on the heart rather than the tumor per se.[15]

Summary

Acute exophthalmos and ophthalmoplegia of the left eye developed in a 58-year-old woman convalescing from a right hemicolectomy for a carcinoid tumor of the colon. Roentgenograms of the orbit and computed tomograms showed a large posterior left orbital mass. Lateral orbitotomy and biopsy confirmed the diagnosis of metastatic carcinoid tumor. Irradiation with radioactive cobalt (^{60}Co) resulted in early relief of the ocular symptoms. To the best of our knowledge, this is the second documented case of orbital metastatic carcinoid tumor and the first patient with orbital involvement from a primary carci-

noid tumor of the colon. Orbital irradiation for metastatic orbital carcinoid tumor has not been previously reported and should be used for symptomatic relief, because long-term survival is possible in patients with metastatic carcinoid tumors.

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CHOROIDAL BLOOD FLOW AS A HEAT DISSIPATING MECHANISM IN THE MACULA

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Between 25 and 33% of all light entering the eye is absorbed by pigment granules in the retinal pigment epithelium and choroid.[1] Part of this absorbed light energy is converted to heat and the amount of heat produced will depend on the light source. If the light source is sufficiently powerful, it can generate temperatures capable of coagulating proteins, producing a typical photocoagulation lesion.

All cellular enzymatic systems are temperature dependent, and most have relatively high temperature coefficients. Variations in local tissue temperature produced by the absorption of light may therefore have a disruptive influence on the balance of normal metabolic activity. Vos[2] proposed that temperatures well below that necessary to produce a photocoagulation lesion can cause "functional" retinal damage by interfering with a cell's metabolic systems, the heat acting as a "metabolic poison."

Tissue temperature has also been implicated as a contributing factor in retinal phototoxicity. Noell and associates[3] were the first to show that light intensities well below that necessary to produce a photocoagulation lesion could cause damage to the retina and retinal pigment epithelium. These changes were reliably produced only when body temperatures were increased. Other investigators[4,5] have confirmed the association of increased body temperature with the severity of light-induced retinal damage. Because increased body temperature alone produced no evidence of retinal damage, it was concluded that the observed effects were caused by light that was potentiated by heat.[4]

Meyer-Schwickerath[6] discussed the effects of applying digital pressure to the eye on the intensity of light needed to produce a photocoagulation lesion. By applying pressure to the globe and presumably decreasing ocular blood flow, a light intensity that was previously subthreshold was now capable of producing a photocoagulation burn. Similarly, Gaerrets and associates[7] were able to produce photocoagulation lesions in dead animals with light intensities well below those necessary in live animals. In both situations the ocular blood flow presumably dissipated the heat generated by the absorption of light. Decreasing the ocular blood flow therefore decreased the light intensity necessary to produce the photocoagulation lesion.

The primary component of the ocular blood flow is the choroidal circulation. It alone accounts for 85% of all ocular blood flow.[8] Per gram of tissue, the choroid has four times the volume of blood flow found in the renal cortex.[8] The choroid is structured so that a dense meshwork of small blood vessels with a large surface

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area, ostensibly for the exchange of oxygen and nutrients, is immediately adjacent to the retinal pigment epithelium and outer retinal layers. However, unlike other circulations, the oxygen content of venous blood in the choroid is exceptionally high, about 95% of that found in arterial blood.[9]

The small amounts of oxygen extracted from blood as it flows through the choroid suggests a role for the high flow choroidal circulation in addition to that of providing oxygen and other nutrients to the outer avascular retinal layers. We studied the possibility that a primary physiologic role of the choroidal circulation is to stabilize the temperature environment of the retina and retinal pigment epithelium.

Material and Methods

Four cynomolgus monkeys were anesthetized with 30 mg/kg of body weight of pentobarbital administered intravenously. One eye of each animal was immobilized by placing traction sutures under each rectus muscle. The animals were then placed in a stereotaxic head holder and the pupils dilated with 10% phenylephrine and 1% tropicamide. Body temperature was held constant by a water profused heat pad and rectal temperature was monitored using a thermistor probe. Blood pressure was monitored by a catheter inserted into the femoral artery. All data were displayed on a strip chart recorder.

A thermistor probe mounted inside the tip of a 23-gauge needle was inserted through the pars plana and positioned under direct ophthalmoscopic control so that its tip was within the retina and choroid, either in the macula or a peripheral retinal site anterior to the equator.

A 27-gauge needle connected by tubing to a reservoir of lactated Ringer's solution was inserted into the anterior chamber of the immobilized eye (Fig. 1).

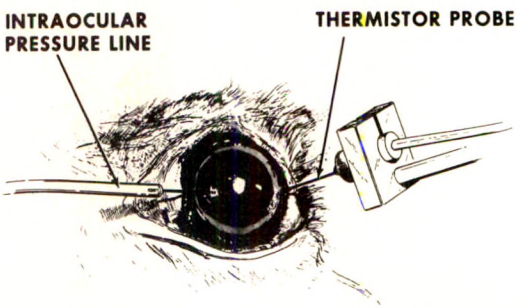

Fig. 1 (Parver, Auker, and Carpenter). Diagrammatic representation of the experimental procedure. A 27-gauge needle inserted through the corneoscleral limbus and connected to a fluid reservoir controls the IOP. The thermistor probe is inserted through the pars plana and directed into the macula under visual control.

Intraocular pressure (IOP) was controlled by varying the height of the reservoir and was monitored by a pressure transducer placed at eye level and connected to the tubing between the needle and the reservoir. The exposed cornea was irrigated with a lactated Ringer's drip.

Temperature recordings were taken from the retina and the choroid in either the macula or a peripheral retinal site anterior to the equator. The IOP was increased from a baseline value of 20 mm Hg. Temperature measurements were taken with the eye exposed to ambient room illumination and then repeated with the eye exposed to a microscope lamp with the intensity control set at 7.5 V and held 20 cm from the eye. This delivered at the corneal surface a light intensity of 1.09 mW/cm^2 at the center spectrum frequency of 675 nm.

Results

Changes in temperature recorded from the retina and choroid paralleled changes in the rectal temperature. Once body temperature stabilized, retinochoroidal temperature stabilized.

Figure 2 shows the temperature responses of two representative animals.

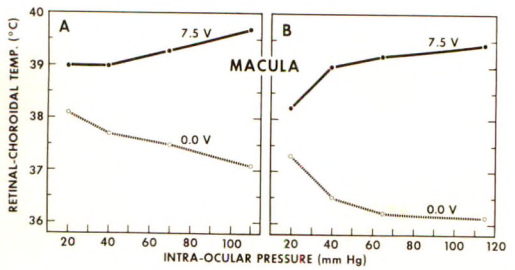

Fig. 2 (Parver, Auker, and Carpenter). Macular temperature as a function of IOP at different light intensities in two representative animals (A and B). Each value was measured not less than one minute after alteration of the pressure at which time the temperatures had equilibrated. Exposed to the 7.5-V light source, increasing the IOP produces an increase in temperature as the IOP is increased (upper solid curves). In contrast, increasing the IOP produces a decrease in retinochoroidal tissue temperature when the eye is exposed only to background room illumination (lower dashed curves).

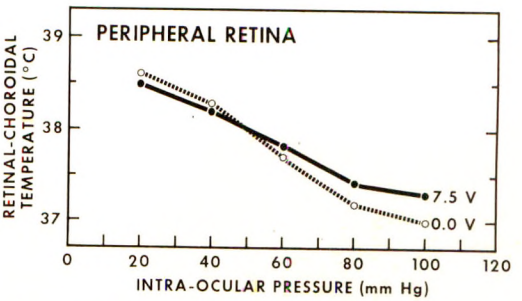

Fig. 3 (Parver, Auker, and Carpenter). Retinochoroidal temperature in a peripheral retinal site as a function of IOP and light intensity. In a peripheral retinal site, increases in IOP produce a corresponding decrease in temperature irrespective of the light source to which the eye is exposed.

The temperature measurements were taken with the animals exposed either to ambient illumination (0.0 V) or a 7.5-V light source. Each value was measured not less than one minute after alteration of the pressure, at which time the temperatures had equilibrated.

The lower curves (0.0 V) in Figure 2 are the responses recorded when the animals were exposed to ambient illumination. All animals showed a decrease in retinochoroidal temperature as the IOP was increased. At the highest pressures used (110 to 115 mm Hg), there was a total decrease in temperature from baseline values (20 mm Hg) of 0.5 to 1.2° C.

With the IOP controlled at 20 mm Hg, there was an initial increase in baseline temperature of 0.5 to 0.9° C when the animals were exposed to the 7.5-V light source. Increasing the IOP produced a further increase in retinochoroidal temperature. The increase in temperature over baseline (20 mm Hg) with the highest IOP used ranged from 0.4 to 0.9° C.

Figure 3 shows the changes in retinochoroidal temperature recorded from a peripheral retinal site. Here, there were no significant increases in baseline temperatures when the eyes were exposed to the 7.5-V light source. Increasing the IOP produced a decrease in the retinochoroidal temperature irrespective of the light source. The decrease in retinochoroidal temperature was slightly less marked with the 7.5-V light source, but ran a parallel course to the changes seen with only background room illumination (0.0 V).

Discussion

All biological systems are sensitive to the temperature environment in which they must function. The retina and retinal pigment epithelium are no exception. These studies suggest that the high flow choroidal circulation normally functions to stabilize the temperature environment for the retinal pigment epithelium and outer retinal layers.

Under most situations, the choroid helps maintain the temperature of the retina and retinal pigment epithelium at or near central body temperature. Without an applied heat load, a decrease in choroidal blood flow will therefore decrease local tissue temperature. Increasing IOP produces a decrease in perfusion

pressure and a corresponding decrease in choroidal blood flow.[8-10]

The focusing of light on the macula by the eyes' optical system presents a unique problem in temperature control. When the eye is exposed to a light source the absorption of focused light by pigment in the retinal pigment epithelium and choroid can, if the applied heat load is sufficient, increase local tissue temperatures above body temperature. Under these conditions, the choroidal circulation acts to limit temperature increases in the macula. The high flow choroidal vascular bed becomes a "heat sink" dissipating heat by convection and conduction through the blood stream.

In those animals exposed to the 7.5-V light source, decreasing the choroidal blood flow by increasing the IOP produces an increase in tissue temperature, shown diagrammatically in Figure 4. This rise in temperature as the choroidal blood flow decreases underscored the importance of the choroidal circulation in dissipating heat generated by the absorption of light.

The increases in retinochoroidal temperature seen in the macula when the eye is illuminated and the choroidal blood flow is decreased are not seen in the retinal periphery (Fig. 3). Even with the eye illuminated, an increase in IOP produces a corresponding decrease in temperature. The focusing of light on the macula and the correspondingly greater increases in temperature explain these differing responses.

Using a relatively low-intensity light source, it was possible in the present study to produce surprisingly significant changes in tissue temperature. Exposing the eye to the 7.5-V (1.09 mW/cm^2) light source resulted in an initial 0.5 to 0.9° C increase in temperature recorded from the macula. After decreasing choroidal blood flow by increasing IOP, the same light source produced an even greater increase in retinochoroidal temperature from 0.9 to 1.8° C (Fig. 2). Although these temperatures are certainly well below those necessary to coagulate proteins, little is known about the possible toxic effects from modest increases in tissue temperature. Vos[2] proposed that relatively small increases in tissue temperature can produce retinal damage via "indirect noxious" effects on metabolic functions. Specifically, he computed that a temperature increase in the range of 2° C could (independent of phototoxic effects) produce the type of damage seen in solar retinopathy.[2]

Recently, Ham and associates[11,12] developed experimental evidence that light in the blue end of the visible spectrum is

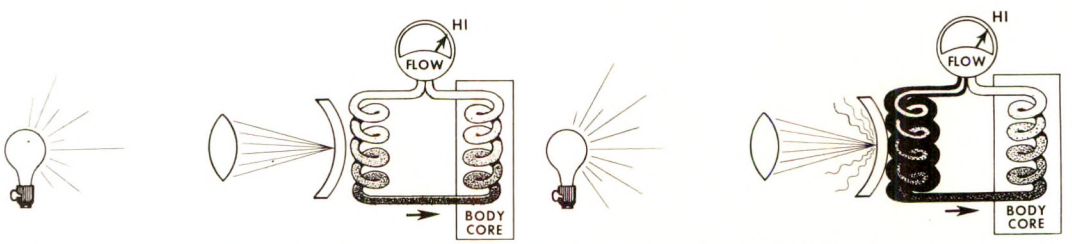

Fig. 4 (Parver, Auker, and Carpenter). Model of function of the retinochoroidal circulation in normal animals and under conditions of thickened choroidal blood vessel walls. Left, Focusing of light on the macula by the eye's optical system produces a local increase in tissue temperature. The high flow choroidal circulation, shown as a coil just behind the retina, absorbs the heat and stabilizes local tissue temperature. The absorbed heat is dissipated by central body mechanisms (body core). Right, Thickening of the blood vessel walls in the choroid decreases the efficiency of the choroidal vasculature in dissipating heat, allowing an increase in tissue temperature.

preferentially toxic to the retina. These observations, coupled with the fact that a large proportion of solar energy is concentrated in the blue end of the spectrum, suggest that the damage seen in solar retinopathy may be produced primarily by short wavelength visible light with thermal enhancement from the longer wavelengths in the visible and near-infrared.

The pathologic changes observed in retinal phototoxicity occur first in the outer segments near the retinal pigment epithelium and choroid, which are the sites of maximum light absorption and therefore heat generation.[3,5,13] Kuwabara and Gorn[13] pointed out that this is unlike other clinical or experimental toxic conditions where the inner segments are more commonly affected. The proximity of the changes in phototoxicity to the region of maximum light-induced heat generation suggests an important thermal influence on phototoxic effects. Although studies of Ham and associates[11,12] provide evidence for a direct toxic effect of light (especially short wavelength visible light) on the retina, it is not clear how essential thermal enhancement is to the phototoxic process.

Little has been published on the possible role of relatively low-intensity light-generated heat as an environmental factor in retinal diseases. One condition in which it may play an important role is involutional macular degeneration. Pathologic studies of the eyes of patients with involutional macular degeneration have shown minimal choroidal changes. One change that has been observed is thickening of the vessel walls in the choroid.[14,15] Because of the high blood flow in the choroid, it is unlikely that these small changes would be sufficient to produce a nutritional deficit to the retinal pigment epithelium and the photoreceptors. Possibly, however, these changes could affect the ability of the choroidal circulation to dissipate heat generated by the absorption of light as suggested by the schema in Figure 4. Even a small increase of temperature over a long period of time may produce damage to the macula by interfering with normal metabolic functions.

The ability of the choroidal circulation to moderate changes in the temperature environment of the retina may be an important factor to be considered not only in macular degeneration but in other retinal and choroidal diseases that predominantly affect the posterior pole.

Summary

We studied the possible role of the choroidal circulation in stabilizing the temperature environment of the retina and the retinal pigment epithelium. Temperature measurements were taken from the retina and choroid of the monkey eye while the ambient illumination and choroidal blood flow were varied. The results showed that the choroidal circulation plays a significant role in dissipating heat generated by the focusing of light at the macula and suggest that this function may be a primary reason for the relatively high values of choroidal blood flow.

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Ophthalmic miniature

Day sight, the nyctalopia of some authors, is said to be endemic in some countries—Poland, the West Indies, Brazil, and various intertropical regions. This affection arises from causes totally different from the former one. Here the eye is habitually exposed to too great a flood of light, whence the retina becomes torpid. It has been said to be endemic in some districts of France, particularly in the neighborhood of Roche Guyon, on the banks of the Seine; but here the soil is of a dazzling white: and as it makes its attacks in the spring, and continues for three months, it is supposed to arise from the keenness of the reflected light, after the dreary winter months.

J. G. Millingen
Curiosities of Medical Experience
London, Richard Bentley, 1839

ANGIOMA-LIKE MASS IN A PATIENT WITH RETROLENTAL FIBROPLASIA

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Previous reports have described the morphologic and pathologic changes of retrolental fibroplasia in its acute and cicatricial stages.[1-6] Late abnormalities associated with retrolental fibroplasia include axial myopia and heterotropia of the macula, as well as rhegmatogenous or combined traction and rhegmatogenous retinal detachment.[7,8] Retinal neovascularization has also been observed during the first and second decades of life in patients with retrolental fibroplasia, although this finding is infrequent. We report herein an unusual retinal mass simulating a capillary angioma in a patient with previously unrecognized retrolental fibroplasia. The lesion was located in the midperiphery at the junction of the posterior (perfused) and peripheral (nonperfused) area of the retina.

CASE REPORT

A 13-year-old boy was first seen here on May 24, 1977, complaining of a mild decrease in vision in the left eye of two months' duration. Previous examination by his primary ophthalmologist on April 5, 1977, had shown a mild vitreous hemorrhage and a red mass in the temporal periphery of the left eye. The mass simulated a retinal capillary angioma, although typical dilated afferent and efferent vessels were absent.

When first seen here, medical history disclosed that the patient had been born at 30 weeks' gestation and weighed 1,092 g at birth. He had received supplemental oxygen therapy during the neonatal period, although exact details were not available. No history of ocular trauma, seizures, or other medical disorders was evident. The patient had no previously diagnosed ocular abnormality other than bilateral myopia, although the left eye had not been correctable to 6/6 (20/20).

Visual acuity was R.E.: 6/6 (20/20) with a −1.25 sphere and L.E.: 6/9 (20/30) with a −1.50 sphere. The eyes were orthophoric, and bifoveal fixation was present. Results of external examination, including pupillary responses, were normal in both eyes. Results of slit-lamp examination of the anterior segment were normal and intraocular pressure measurements were also normal.

Ophthalmoscopy of the right eye showed absence of the retinal vasculature anterior to the equator in the temporal quadrants, although there was no distortion of the posterior retinal vasculature. Ophthalmoscopy of the left eye showed a thin epiretinal membrane covering the macula. The thickest portion of the membrane was inferotemporal to the macula, but there was no distortion or temporal dragging of the posterior retinal tissue (Fig. 1). In the midperipheral portion of the temporal fundus, a globular mass was present that projected from the retina into the vitreous (Fig. 2). The lesion was pink-red in color, and some hemorrhage was present over the surface of the lesion and in the adjacent vitreous gel. The peripheral portion of the temporal retina was avascular; the mass was located at the junction of the vascular and avascular zones.

Fluorescein angiography showed abnormal dilation of the larger retinal vessels and capillary bed along the boundary between the perfused and nonperfused portions of the retina (Fig. 3). Moderate fluorescein leakage from the capillary bed in an area slightly superior to the red mass indicated retinal neovascularization. Fluorescein leakage also oc-

Fig. 1 (Barr, Rice, and Michels). The left macula has a preretinal membrane with minimal distortion of the posterior vasculature.

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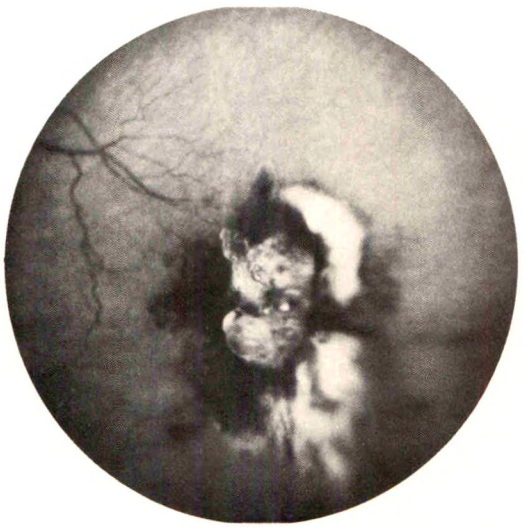

Fig. 2 (Barr, Rice, and Michels). Elevated angioma-like mass in temporal periphery of the left eye, with surrounding retinal and vitreous hemorrhage.

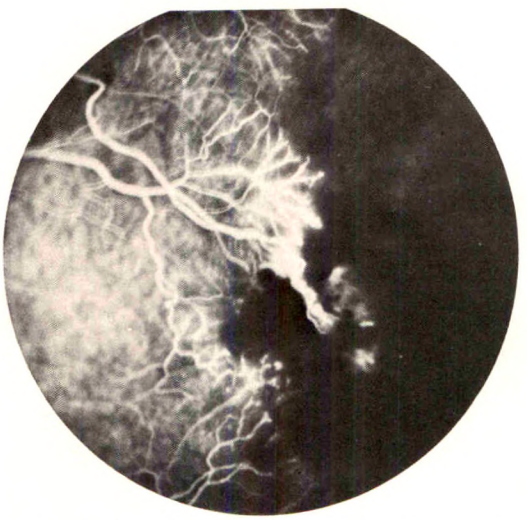

Fig. 3 (Barr, Rice, and Michels). Early-phase fluorescein angiogram shows tumorlike mass at junction of vascular and avascular zones of temporal retina. Note neovascularization, with vessel extending into the lesion superiorly.

curred within the tissue mass, although there was little increased fluorescence in the later stages of the angiogram (Fig. 4). No abnormality of the vascular pattern or leakage of fluorescein dye was noted in the posterior pole. A diagnosis of retrolental fibroplasia with peripheral neovascularization and preretinal and vitreous hemorrhage was made.

The vascular lesion was later treated by argon laser photocoagulation, applied by the patient's referring ophthalmologist. The lesion was first surrounded with photocoagulation burns, and later the lesion itself was treated in a separate session. At follow-up examination one year later visual acuity with correction was R.E.: 6/6 (20/20) and L.E.: 6/7.5 (20/25); the peripheral retinal neovascularization, angioma-like mass, and hemorrhage were completely replaced by a pigmented chorioretinal scar (Fig. 5).

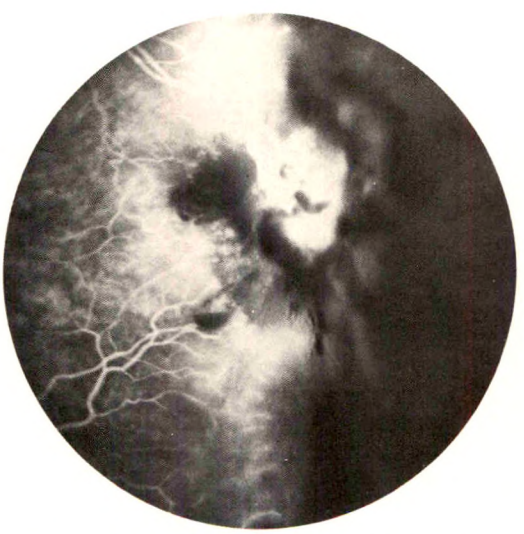

Fig. 4 (Barr, Rice, and Michels). Late-phase angiogram shows moderate staining of the lesion, partly obscured by surrounding hemorrhage, and moderate leakage from areas of neovascularization.

Discussion

In the normal human eye, the retina becomes vascularized during the third trimester of gestation. This normal vascularization progresses from the optic nerve toward the periphery and, with full-term gestation, is completed at the time of birth. In premature infants, however, the peripheral retina is incompletely vascularized at birth. Retrolental fibroplasia is a well-recognized proliferative retinopathy that occurs most commonly in premature infants as a response of immature retinal vessels to vasospasm, induced by increased arterial oxygen tension, and followed by a secondary relative retinal hypoxia.

The acute changes of retrolental fibroplasia include a spectrum of abnormalities that begin with abnormal proliferation of retinal vascular tissue at the

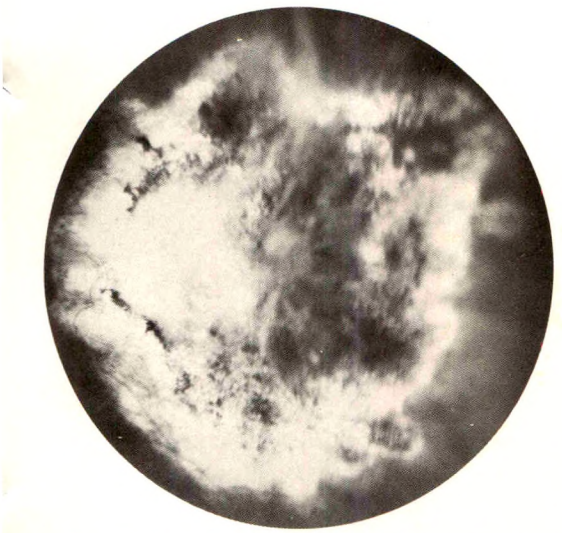

Fig. 5 (Barr, Rice, and Michels). Angioma-like lesion, one year after argon-laser photocoagulation.

junction of the vascularized and nonvascularized portion of the retina forming a circumferentially oriented ridge.[3-5] This may progress to total traction retinal detachment,[7] although the proliferative process eventually becomes inactive without blinding complications in 80 to 90% of eyes affected with retrolental fibroplasia.[9] In some eyes, the proliferative tissue causes tangential traction on the posterior retina, with dragging of the vessels and heterotropia of the macula, although normal or near-normal vision may be present. Therefore, the changes of previously regressed retrolental fibroplasia are sometimes asymptomatic and they may remain unrecognized.

In our patient the history of prematurity, low birth-weight, and supplemental oxygen therapy were initially overlooked because of the nearly normal vision and the lack of vascular abnormalities affecting the posterior retina. However, Tasman[7] found physical evidence of inactive retrolental fibroplasia in nine (20%) of 46 seemingly normal school-age children with normal or near-normal vision and a history of prematurity. Moreover, he noted that distortion of the posterior retina occurred in only 30% of 39 other patients (21 of 69 eyes) studied to evaluate late vitreoretinal changes in the inactive stage of this disease.

Although late retinal neovascularization is recognized to be an infrequent finding in eyes with otherwise inactive retrolental fibroplasia, the angioma-like abnormality present in our case has not been previously reported. This red, ovoid mass was located at the junction of the vascularized and nonvascularized retina, and was adjacent to areas of retinal neovascularization. Although parts of the lesion were nonfluorescent on fluorescein angiography, the angiogram did show mildly dilated retinal vessels entering the mass, and there was fluorescein leakage within portions of the mass. These features suggest that the lesion was made up in part of neovascular tissue, although some of the lesion was partially organized hemorrhage.

A preretinal membrane partly covering the left macula was also a prominent feature in our patient. This finding has not previously been reported in other patients with similar general features of inactive retrolental fibroplasia. However, such epiretinal membranes are not uncommon, and can occur in a variety of disorders, including retinal vascular malformations.[10] Although these epiretinal membranes are rarely seen in patients with inactive retrolental fibroplasia, abnormalities of the posterior pole are often present. Pigmentary changes, usually consisting of a fine pigment proliferation, may occur in up to 40% of these eyes.[8]

The differential diagnosis of retinal neovascularization is not always clear. It may occur in various conditions that share the common abnormality of areas of retinal nonperfusion and presumed retinal hypoxia. These disorders are caused by a variety of mechanisms, which include the following: (1) inadequate afferent blood supply to the eye, such as in occlusive carotid or ophthalmic artery disease, with venous stasis

retinopathy; (2) abnormalities of the blood predisposing to intravascular occlusion, such as macroglobulinemia or sickle hemoglobinopathy; (3) possible abnormalities of the blood-vessel wall, such as diabetic retinopathy; and (4) obstruction of the venous outflow, such as retinal branch-vein obstruction.

The ophthalmoscopic abnormality in our patient is similar to changes seen in sickle-cell hemoglobin retinopathy, in which peripheral retinal neovascularization occurs at the junction of the perfused and nonperfused portions of the retina, and organizing preretinal exudate and hemorrhage are not unusual.[11,12] We have also observed similar neovascularization in a patient with Eales' disease. Because this type of neovascular change is nonspecific, evaluation of each case requires appropriate history, thorough examination of both eyes, and systemic evaluation, with special laboratory tests in certain circumstances.

The treatment of symptomatic retinal neovascularization is usually photocoagulation. Flat neovascular tissue can be treated directly by applications that are intense enough to cause intravascular coagulation. Retinal neovascularization may regress in response to adjacent photocoagulation used to devitalize nearby areas of nonperfused retina. This works by the presumed mechanism of destroying hypoxic retinal tissue that is thought to produce a substance capable of causing neovascular proliferation, and is necessary to maintain perfusion of the new blood vessels. In our patient, the areas of retinal neovascularization were treated directly, and this was effective.

Summary

A 13-year-old boy had mild vitreous hemorrhage in the left eye, and a red angioma-like epiretinal mass in the equatorial zone of the temporal fundus. The retina anterior to the mass was nonvascularized, and similar nonvascularization of the pre-equatorial retina was present in the temporal quadrants of the fellow eye. Fluorescein angiography showed intraretinal neovascularization along the margin of the perfused and nonperfused retina and leakage from portions of the angioma-like mass, suggesting that it was composed of neovascular tissue and adjacent hemorrhage. The patient had been a premature infant, with a birth weight of 1,092 g, supporting the presumptive diagnosis of previously asymptomatic retrolental fibroplasia. Photocoagulation was successful in obliterating the neovascular tissue.

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SECONDARY ANGLE-CLOSURE GLAUCOMA IN CICATRICIAL RETROLENTAL FIBROPLASIA

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There has been little published on secondary angle-closure glaucoma, an unusual complication of cicatricial retrolental fibroplasia.[1-5] McCormick and Pratt-Johnson[6] reported one case of retrolental fibroplasia with bilateral secondary angle-closure glaucoma. Collyer, Arstikaitis, and Pashby[7] briefly mentioned two eyes with retrolental fibroplasia complicated by glaucoma. Cohen and associates[8] reported on 54 eyes of 27 patients with retrolental fibroplasia; the anterior chamber was shallow in 21 eyes and entirely obliterated in 14 eyes. There was one phthiscal eye after surgery for secondary glaucoma. The authors do not mention the modality of treatment for this patient.

I studied five patients who had secondary angle-closure glaucoma in relationship to cicatricial retrolental fibroplasia.

CASE REPORTS

Case 1—A 5-month-old boy weighed 1,400 g at birth after a seven-month pregnancy with a normal vaginal delivery. He spent 66 days in the hospital after birth and received oxygen during most of this period. Examination at this time showed horizontal jerk nystagmus. The patient was unable to follow light or toys. He did close his eyes when stimulated with the bright light from the indirect ophthalmoscope. His pupils dilated 8 mm and a dense white mass was located behind the lens in both eyes with a large number of vessels located in the center of the mass. The lenses were noted to be clear. No normal retinal details could be seen. A diagnosis of retrolental fibroplasia was made. The patient was again seen at age 2 years. He had mild cataractous changes in the lens of the right eye. When he returned one month later, his mother said he had become irritable over the past several days. Examination at this time showed that he had no anterior chamber in the right eye, but he had a densely cataractous lens and epithelial corneal edema. He was taken to surgery the next day. While the infant was under general anesthesia intraocular pressure (IOP) by Schiøtz tonometry was R.E.: 32 mm Hg and L.E.: 14.6 mm Hg. A pars plana lensectomy and anterior vitrectomy were performed on the right eye with the Douvas Roto-extractor. The postoperative course was uneventful. Six months later he had a deeply formed anterior chamber in the right eye with visual acuity of light perception. He has no pain in the right eye.

Case 2—A 2-year-old girl weighed 1,008 g at birth. She was the product of a five-month pregnancy. She was hospitalized for two months after birth and received oxygen throughout her stay. She had horizontal jerk nystagmus in both eyes. She had an alternating esotropia of 25 prism diopters at distance and near and shallow anterior chambers with dense cataracts in both eyes. No epithelial edema was present. Behind both lenses was a dense fibrous mass that occupied the entire vitreous cavity. No discernable retinal details could be seen. Two months later, the patient had no anterior chamber on the right side associated with epithelial corneal edema. Two days later the patient had a pars plana lensectomy and anterior vitrectomy performed with the Douvas Roto-extractor. Preoperative IOP with the Perkins tonometer was R.E.: 38 mm Hg and L.E.: 16 mm Hg. One month later, the anterior chamber was completely gone in the left eye. No corneal epithelial edema was present. The patient was again taken to surgery where IOP with the Perkins tonometer was 18 mm Hg in the right eye and 36 mm Hg in the left eye. A pars plana lensectomy and anterior vitrectomy were performed on the left side. A two-year follow-up examination showed visual acuity of light perception. However, both anterior chambers are deep, and the patient has no pain in either eye.

Case 3—An 11-month-old girl weighed 1,428 g at birth. She was born in Thailand and had received oxygen for 26 days after birth. Examination of her eyes showed shallow anterior chambers with horizontal jerk nystagmus bilaterally. Retinal details could be seen. There was temporal dragging of both optic nerves and a dense vitreoretinal mass peripherally located in the temporal aspect of both eyes. The diagnosis of cicatricial retrolental fibroplasia was made. The patient was followed up conservatively, and 14 months later she had corneal edema on the left side with no anterior chamber. Early posterior subcapsular cataractous changes were noted in the left eye only. The right eye had a shallow anterior

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chamber. Two days before her visit to the ophthalmologist, she had become completely introverted, had begun crying, and would not eat. She was vomiting three to four times per day. She was taken to surgery six hours later. With the patient under general anesthesia IOP by Schiøtz tonometry was 36 mm Hg in the left eye and 14 mm Hg in the right eye. A pars plana lensectomy and vitrectomy were performed with the Ocutome system. Within six hours after surgery, the child was taking fluids and was playful and happy. A two-year follow-up showed her to have visual acuity of hand motions in both eyes. There is a deep anterior chamber in the left eye and a shallow anterior chamber in the right eye. There has been no episode of acute glaucoma in the right eye.

Case 4—A 3½-year old boy weighed 1,036 g at birth. He had been hospitalized for one month after birth and had received oxygen. The anterior chambers were extremely shallow bilaterally and visual acuity was light perception. Dense retrolental masses were present bilaterally and no retinal details could be seen in either eye. The patient returned one month later with acute corneal edema in the right eye and no anterior chamber. Mild posterior subcapsular changes were present in the right eye. Applanation pressure was 38 mm Hg in the right eye and 14 mm Hg in the left eye. On the following day the patient was taken to surgery where a pars plana lensectomy and vitrectomy were performed. The Ocutome system was used. A one-year follow-up showed this patient to have visual acuity of only light perception in both eyes. He has a deep anterior chamber in the right eye, and a shallow anterior chamber in the left eye. He has no pain in either eye.

Case 5—A 3½-year old boy weighed 1,232 g at birth. He had a red inflamed right eye for three days before his office visit. Ocular examination showed no anterior chamber on the right side with 4+ epithelial edema. A shallow anterior chamber was present in the left eye but there was no epithelial edema. Retrolental masses were present bilaterally. Retinal details could not be seen in either eye. The pupil in the right eye was fixed at a mid-dilated point at approximately 6 mm and was unreactive to light. With the patient under general anesthesia, a pars plana lensectomy and anterior vitrectomy were performed with the Ocutome system. At surgery, IOP via the Perkins tonometer was 40 mm Hg in the right eye and 16 mm Hg in the left eye. A one-year follow-up showed a deep anterior chamber on the right side and a shallow anterior chamber on the left side. The patient had no pain in either eye. Visual acuity is light perception in both eyes.

Discussion

The active phase of retrolental fibroplasia lasts from three to six months. This is followed by a cicatricial stage. Cicatricial retrolental fibroplasia has many characteristic findings that include the following: dragging of the optic nerve, retinal folds, proliferation of the retinal pigment epithelium, chorioretinal scarring, and vitreous membranes.[9]

Children with retrolental fibroplasia need to be followed up routinely, because they are prone to secondary complications. All five of these children manifested glaucoma after the age of 2 years. Each child had received large amounts of oxygen and each child had a below normal birth weight. The mechanism of the glaucoma was a pushing forward of the lens iris diaphragm secondary to the retrolental mass. This pushing forward caused a secondary angle-closure glaucoma.

Each patient was successfully managed by a pars plana lensectomy and anterior vitrectomy that alleviated the glaucoma. Lensectomy and anterior vitrectomy were believed to be a definitive method of treating this particular problem. The visual results have not been good in any of these patients. However, the results have been successful, because the children have retained their eyes without pain or glaucoma.

All of these children were extremely ill at the time of their angle-closure attack. They had stopped eating and were not drinking fluids. Although some of these cases might have stabilized at a normal pressure or proceeded into hypotony or phthisis, surgery was believed to be indicated because of the illness of the patients. Blodi[10] warned of possible disastrous complications in the opening of an eye in such patients; however, these children have done well. Although secondary angle-closure glaucoma has occurred bilaterally in only one of these patients, a close follow-up must be maintained for the occurrence of this disorder in the fellow eye. All the patients had extremely poor visual acuity in the range of light perception to hand motions. Because of this, the small risk of sympathetic ophthalmia was not believed to be

strong enough to dissuade me from performing surgery. However, there are many well-documented cases of severe retrolental fibroplasia in one eye with relatively mild involvement of the fellow eye. If secondary angle-closure glaucoma should develop in a patient whose involved eye is blind or nearly blind with a useful fellow eye, alternatives to intraocular surgery should be considered because of the possibility of sympathetic ophthalmia. Enucleation, retrobulbar alcohol, and cyclocryotherapy should be investigated in these situations.

Summary

Five patients had cicatricial retrolental fibroplasia with a complication of secondary angle-closure glaucoma. In all the patients, the glaucoma occurred after age 2 years. All were treated with a pars plana lensectomy and anterior vitrectomy, which alleviated the glaucoma. They all achieved normal intraocular pressure and a pain-free eye. However, visual acuity was poor, in the range of light perception to hand motions. All patients have been followed up for one year and in only one patient has the fellow eye developed secondary angle-closure glaucoma.

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RETINAL INJURIES ASSOCIATED WITH CATARACT SURGERY

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Retinal injuries and subsequent retinal detachment can occur as a complication of any type of ocular surgery.[1-4] Aphakic eyes are more prone to develop retinal detachment than phakic eyes,[5] with reported incidences of up to 3.5%.[6] Hagler[7] has stated that, " . . . aphakia is a major associated finding, if not the actual cause, in retinal detachments undergoing surgery." In most cases, although the association of retinal detachment with cataract surgery is present, the specific causal injury to the retina is unknown or uncertain. We describe four cases of retinal detachment and one case of retinal perforation where the cause is known.

SUBJECTS AND METHODS

Cases were selected from the files of the Retina Services of the Mount Sinai Hospital and Medical Center, St. Luke's Hospital Medical Center, Lenox Hill Hospital, and our private office records. Each patient underwent a complete ophthalmologic examination including indirect ophthalmoscopy and scleral depression. A detailed retinal drawing was also made of each case.

CASE REPORTS

Case 1—A 66-year-old woman was admitted to the hospital for cataract extraction of the left eye under local anesthesia. An inferior retrobulbar injection was given using a blunted 24-gauge needle. The same needle was then used for a superior retrobulbar injection. While the superior retrobulbar injection was being administered, the patient began to move about and became restless. She complained of pain and appeared agitated. Surgery was cancelled and was rescheduled for another day under general anesthesia.

The following day the patient had moderate ocular discomfort and was noted to have left conjunctival ecchymosis. Ophthalmoscopic examination showed a vitreous hemorrhage with a small hemorrhage nasal to the disk and a larger one inferiorly near the equator at 6 o'clock. Superiorly, two small round retinal holes were seen (Fig. 1). It was believed that these retinal holes represented the entrance and exit site of the retrobulbar needle when it inadvertently perforated the globe.

Ten days after the first surgery, retinocryopexy was performed through a conjunctival incision to close the two superior breaks. Six weeks after the cryopexy, successful intracapsular cataract surgery was performed under general anesthesia. The patient has been followed up for five years. She is asymptomatic and has maintained visual acuity of 6/9 (20/30).

Case 2—A 32-year-old man with severe myopia underwent cataract extraction in the left eye under local retrobulbar anesthesia administered with a blunted 24-gauge needle. Two weeks postoperatively, ophthalmoscopic examination showed a vitreous hemorrhage with a retinal detachment extending to the macula. The appearance was that of retinal incarceration with a small round hole and radiating

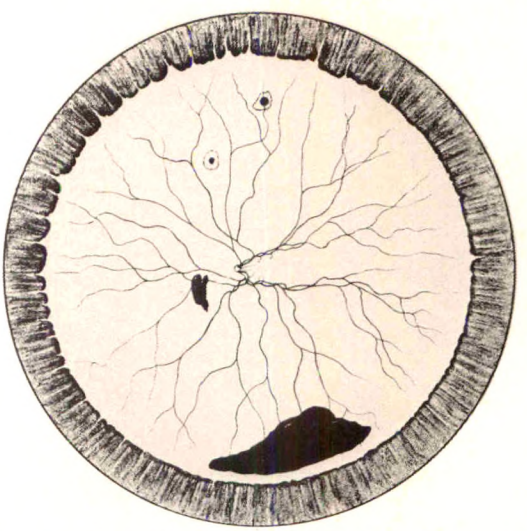

Fig. 1 (Seelenfreund and Freilich). Case 1. Retinal drawing of left eye showing retinal and choroidal perforations superiorly. Vitreous and preretinal hemorrhages are also present inferiorly.

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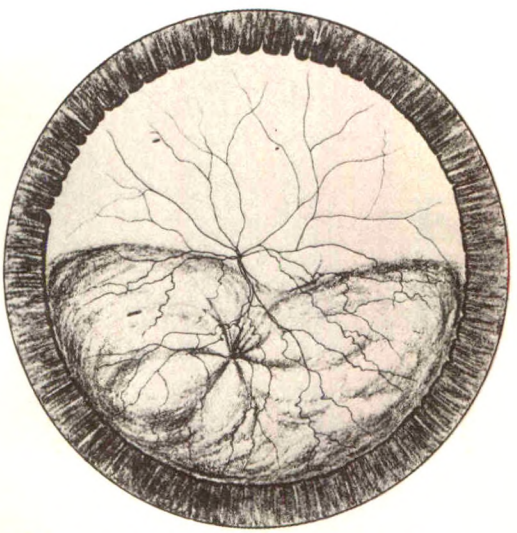

Fig. 2 (Seelenfreund and Freilich). Case 2. Retinal drawing of left eye showing vitreous hemorrhage and an inferior retinal detachment with a posterior hole. There are radiating retinal folds from the hole giving the appearance of retinal incarceration.

folds (Fig. 2). It was believed that this hole was probably produced by the retrobulbar needle.

The corneoscleral wound was allowed to heal and five weeks after cataract operation a scleral buckling procedure was performed. The retinal hole was localized 23 mm from the corneoscleral limbus posterior to the exit of a vortex vein. A thin layer of scar tissue was present on the sclera under the retinal hole covering a small scleral perforation. The retinal hole was surrounded with cryotherapy under direct visualization. A hard silicone explant with an encircling silicone band was placed and subretinal fluid was drained. The retina reattached with return of visual acuity to 6/7.5 (20/25) corrected with a contact lens. The retina has remained in place for 6 ½ years.

Case 3—An 81-year-old woman underwent intracapsular cataract extraction that was said to be uneventful. One day postoperatively she was noted to have a soft eye with a large choroidal detachment and an overlying flat retinal detachment. Three weeks later, when the choroidal detachment had not absorbed, a retinal consultation was requested.

Examination at that time showed a large nasal and temporal choroidal detachment. There was no leak from the corneoscleral wound. The retina was moderately elevated inferiorly and a few fixed retinal folds were present in the posterior pole. No retinal holes were found and scleral depression was not performed because the corneoscleral wound was still not completely healed. Because of the generally poor prognosis in patients with retinal detachment accompanied by choroidal detachment,[8,9] the choroidal detachment was allowed to absorb before retinal surgery was performed. It took an additional three weeks for the choroidal detachment to absorb and by then a total retinal detachment was present.

At the time of retinal surgery when the recti muscles were being isolated, a small scleral perforation mark was found just posterior to the nasal edge of the insertion of the superior rectus muscle. A second scleral perforation site was found posterior to the lateral edge of the superior rectus muscle insertion (Fig. 3). It was believed that these perforations had occurred when the bridle suture was placed during the cataract surgery. Indirect ophthalmoscopy using scleral depression showed two small horizontal tracks in the choroid corresponding to the areas of scleral perforation with a small retinal hole in the temporal track. No other retinal holes were seen (Fig. 4).

A scleral buckling operation using cryotherapy, a buried silicone implant and encircling band, with drainage of subretinal fluid was performed without complication. The areas of scleral perforation were not dissected in preparing the scleral bed. At the time of surgery the retina was reattached but the fixed folds over the posterior pole persisted. Postoperatively, the patient again developed a moderate choroidal detachment that persisted for ten days and then slowly absorbed. The retina redetached with fixed retinal folds and further surgery was not advised.

Case 4—A 72-year-old woman underwent cataract surgery in the right eye under local anesthesia. The lens was delivered intracapsularly followed by loss of vitreous. A 19-gauge needle attached to a 5-ml syringe was placed in the center of the vitreous cavity and a small amount of liquid vitreous was removed.

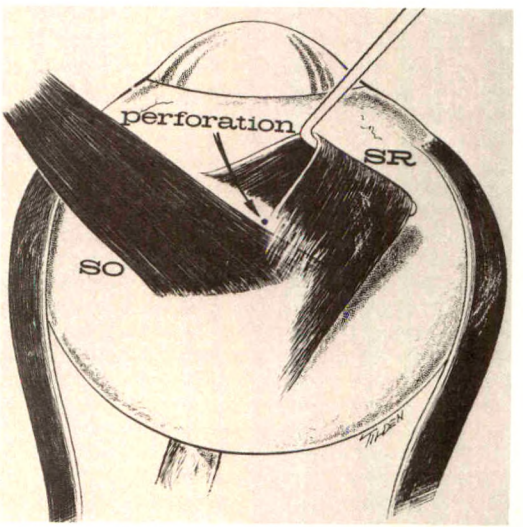

Fig. 3 (Seelenfreund and Freilich). Case 3. Superior rectus muscle (SR) is elevated to show the perforation of the sclera at the nasal edge of the muscle. A similar perforation site was seen on the temporal edge of the superior rectus muscle anterior to superior oblique (SO) muscle.

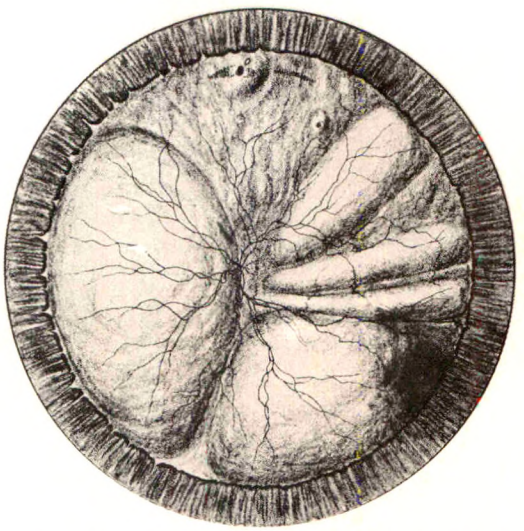

Fig. 4 (Seelenfreund and Freilich). Case 3. Retinal drawing of left eye showing a total retinal detachment with a small retinal hole at the 11:30 meridian and needle tracks in the underlying choroid.

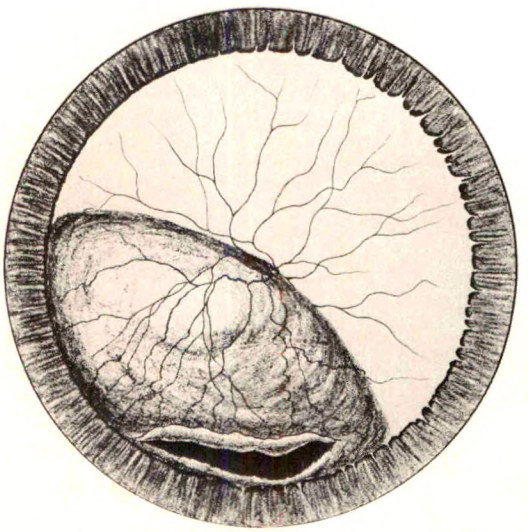

Fig. 5 (Seelenfreund and Freilich). Case 4. Retinal drawing of right fundus four weeks after attempt to aspirate vitreous with an 18-gauge needle during cataract surgery. A large dialysis with an inferior retinal detachment is present.

The needle was then directed toward the inferior vitreous cavity and firm suction on the syringe showed only solid vitreous to be present. Some of this was aspirated into the syringe. The needle was removed, the anterior chamber was carefully cleaned, and the corneoscleral wound was closed.

Three weeks after surgery visual acuity was 6/21 (20/70), but this suddenly decreased to hand movements one week later. Indirect ophthalmoscopic examination showed an inferior retinal detachment with a large dialysis from 4:30 to 7 o'clock (Fig. 5).

Five weeks after cataract extraction the patient underwent a scleral buckling operation. A buried silicone implant was placed from 4 to 8 o'clock with an encircling silicone band. Cryoprobe applications were placed in the scleral bed and perforation for subretinal fluid was performed. The retina reattached, but the patient only regained visual acuity of counting fingers. The retina has remained attached for two years; however, preretinal membranes have developed over the superior retina causing areas of wrinkling. The long-term prognosis is uncertain.

Case 5—A 54-year-old man was undergoing cataract extraction in the right eye under local anesthesia. Just after the lens was removed intracapsularly with a cryoprobe, he had an expulsive choroidal hemorrhage with loss of a large amount of vitreous, and a choroidal mass with overlying retina was present in the pupillary space. A stab incision made into the sclera temporally for release of the choroidal hemorrhage was successful. The suprachoroidal blood was released and the retina settled back into the vitreous cavity. The anterior chamber was cleaned, the corneoscleral wound was closed, and the globe reconstituted with saline.

Postoperatively, when the vitreous cavity cleared, large choroidal detachments were noted. These slowly resorbed and six weeks later visual acuity was 6/30 (20/100) with a +10 diopter lens. Retinal examination at that time showed a temporal retinal dialysis with a localized detachment under the area where the stab incision had been made (Fig. 6).

Two months after the cataract operation, a scleral buckling procedure using a buried silicone implant and an encircling band was performed without complication. The retina reattached and has remained in place with retention of visual acuity of 6/18 (20/60) for two years.

Discussion

These five cases show that complications can occur during any phase of cataract surgery even before the anterior chamber has been entered. They emphasize the need for care and caution in even the most routine cataract operation.

Atkinson[10] does not mention the problem of perforation of the globe with a retrobulbar needle. In our first two cases the perforation occurred despite the use of a blunted retrobulbar needle. In Case 1, the perforation occurred during the superior retrobulbar injection. The patient immediately reacted with pain and restlessness. This alerted the surgeon not

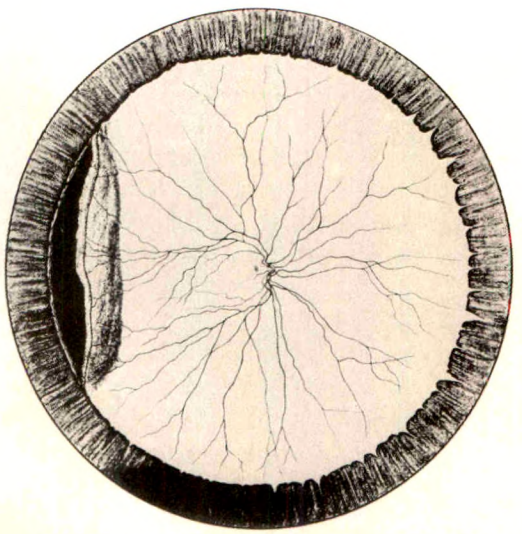

Fig. 6 (Seelenfreund and Freilich). Case 5. Retinal drawing of right fundus six weeks after stab incision to relieve expulsive choroidal hemorrhage. There is a temporal dialysis with an overlying localized retinal detachment.

to proceed any further. He did not realize that the needle had perforated the globe until the following day when the patient was less agitated and could be examined with an indirect ophthalmoscope. In Case 2, the patient had severe myopia (−14 diopters), and had an elongated globe. In this case the surgeon did not realize that the perforation had occurred and he continued with the cataract surgery. This eventually led to a retinal detachment. Therefore, when operating on a patient with severe myopia who may have an elongated eyeball, the possibility of perforation is greater and the surgeon should take greater care in administering the retrobulbar block.

In Case 3, the surgeon was completely unaware that the bridle suture needle had perforated the globe. The eye was hypotonous postoperatively and the persistence of the choroidal detachment was unusual for an eye that had undergone uneventful surgery. A suture needle should never be forced through ocular tissues. This is especially true when muscles are grasped through intact conjunctiva as is frequently done when placing a bridle suture or placing a stay suture for a cryopexy or a retinal procedure.

In another case the bridle suture perforated the globe during cataract surgery. In this case the surgeon recognized the problem when the eye suddenly became hypotonous after the bridle suture was placed, but completed the cataract surgery anyway. The perforations sealed themselves and postoperatively the patient developed an endophthalmitis. This patient had undergone previous ocular surgery and the superior rectus muscle adhered to the sclera. Therefore, when the surgeon tented up the muscle with forceps, the sclera was probably also elevated, allowing the needle to puncture the globe. The cataract surgeon must be aware of the possibility of muscle-scleral adhesions in eyes that have undergone previous surgery and make certain the muscle is free of sclera before placing the bridle suture.

When vitreous rises and is present in the anterior chamber or is lost, many surgeons place a needle in the vitreous cavity to withdraw liquid vitreous. This often permits the remaining vitreous to settle back behind the iris diaphragm. Problems occur when the pocket of liquid vitreous can not be easily found or if there is liquid vitreous it may only be a small amount. Vigorous aspiration in these circumstances will pull on formed vitreous that may still be attached to the peripheral retina as occurred in Case 4. The surgeon, therefore, should aspirate slowly and gently. If possible, a vitreous instrument that cuts the vitreous before aspirating should be available in the operating room and cataract surgeons should be familiar with its use.[11]

Expulsive choroidal hemorrhages always present a difficult problem. The events occur with such rapidity that the surgeon is usually surprised. One sur-

geon we know who has successfully treated several of these cases advocates closing the corneoscleral wound as quickly as possible in order to tamponade the wound and build up pressure to stop the hemorrhage (H. Schneider, personal communication, June 1979). Other cataract surgeons advocate incising the sclera to the suprachoroidal space to release the suprachoroidal hemorrhage and therefore decrease the accompanying pressure on the inside of the eye. Case 5 is unusual in that the patient's eye recovered useful vision after this severe complication. The surgeon examined the fundus after the hemorrhage cleared and was able to detect a retinal dialysis in the area in which he made a stab incision.

Recent studies[12,13] have shown that good visualization of the fundus can be obtained with an indirect ophthalmoscope immediately after cataract surgery on the operating room table. Postoperatively, the patient is more resistant to indirect ophthalmologic examination. Therefore, if there is the possibility of a complication or if the operative procedure has not proceeded as it should, the retina should be examined with an indirect ophthalmoscope on the operating room table. This can be accomplished with little or no manipulation and useful information can be obtained at an early stage.

Summary

Five patients had trauma to the retina that occurred during cataract surgery. In two of the cases the injury was caused by perforation of the globe by the retrobulbar injection needle and in one case the retinal injury occurred when the superior rectus muscle bridle suture perforated the sclera. A stab incision for release of blood in an expulsive choroidal hemorrhage caused a retinal dialysis. Another case of retinal dialysis was caused by aspiration of solid vitreous after vitreous loss.

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INTRAOCULAR GAS INJECTION IN THE PSEUDOPHAKIC PATIENT

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Implantation of an intraocular lens after cataract surgery is an increasingly popular procedure in the United States. After such implantation, retinal detachment surgery has been successful.[1] Injection of gas (air or sulfur hexafluoride [SF_6]) into the vitreous cavity can be most valuable in helping to seal certain retinal breaks.[2] However, injection of gas behind an intraocular lens may lead to shallowing of the anterior chamber and even contact with the corneal endothelium.

We report a case of corneal decompensation following intraocular lens-cornea contact after gas instillation and show in another case a surgical procedure designed to alleviate this problem.

CASE REPORTS

Case 1—A 72-year-old man had a cataract extraction and an intraocular lens placed in his left eye nine months before he was seen by us. Blunt trauma had resulted in vitreous hemorrhage and increased intraocular pressure (IOP) six months before this examination, and after appropriate evaluation, elective vitrectomy was agreed on to try to improve his visual acuity of light perception. Preoperatively, the cornea was clear except for epithelial edema consistent with increased IOP of 50 mm Hg. The anterior chamber was deep, and a four-loop lens was in place.

At the end of vitrectomy, a retinal dialysis was seen near the sclerotomy. After performing cryoretinopexy and buckling the area, SF_6 gas was instilled into the vitreous cavity. One and a half milliliters of fluid was first removed from behind the pseudophakos, and an equal amount of 100% SF_6 gas was instilled. The pseudophakos immediately contacted the corneal endothelium and did so intermittently during the following three days (Fig. 1). Subsequently, with retinal attachment and otherwise clear media, the cornea decompensated, showing stromal thickening, epithelial edema, and peripheral neovascularization, despite normal IOP. A means of protecting the corneal endothelium was necessary in this case.

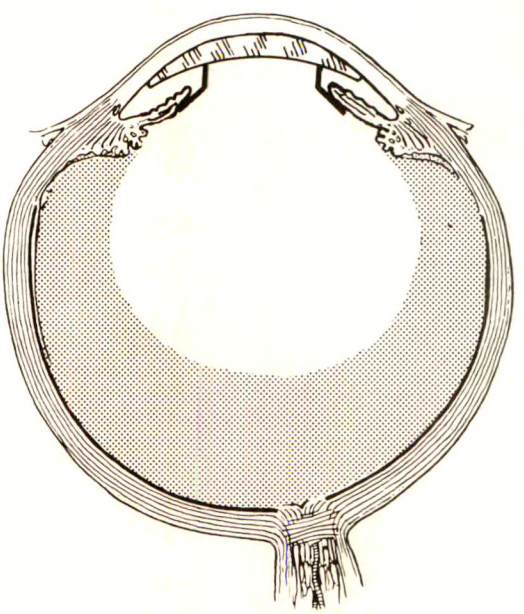

Fig. 1 (Diddie and Smith). The pseudophakos, elevated by the gas bubble in the vitreous cavity, contacts the corneal endothelium.

Case 2—A 62-year-old man had cataract surgery and intraocular lens placement in the right eye three months before coming to our clinic. At the initial visit, he had a history compatible with a month-old retinal detachment in the right eye. Visual acuity was light perception in the right eye as a result of a total retinal detachment with fixed folds radiating back to the optic nerve. The anterior chamber was formed and a two-loop iridocapsular-fixated pseudophakos was in place.

At surgery, vitrectomy and scleral buckling were done. We next expressed aqueous fluid from the anterior chamber and replaced it with 0.5 ml of SF_6 gas, using the technique described in the Material and Methods section. Fluid and gas were then sequentially withdrawn from and injected into the vitreous cavity. The pseudophakos did not touch the endothelium during the recovery period. Despite a recurrence of the periretinal proliferation, the cornea remained clear and did not decompensate.

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Material and methods

The corneal endothelium is protected from contact with the intraocular lens by a bubble of gas. Before injection of gas into the vitreous cavity, two 27-gauge needles are inserted through clear cornea close to the corneoscleral limbus near the horizontal meridians. Aqueous fluid is allowed to drain from one needle while SF_6 or air, or a mixture of the two, is injected through the other needle (Fig. 2). Approximately 0.5 ml of gas is instilled rapidly as a bolus. The rapid injection, resulting in one large gas bubble, eliminates the visual distortion of multiple small bubbles. Both needles are then withdrawn.

With cornea thus protected, a single 27-gauge needle is passed through the pars plana and the needle tip positioned in the pupil. We use two 5-ml syringes, attached to the needle by a three-way stopcock, to remove fluid from the vitreous cavity, and then to replace it with an equal volume of pure SF_6 gas, air, or gas-air mixture (Fig. 3). Postoperatively, the patient is positioned so the posterior gas bubble properly tamponades the retinal break. After the first few critical days, the anterior gas bubble resorbs, but the posterior bubble resorbs as well, and with the proper positioning of the patient's head, endothelial touch can be avoided.

Discussion

Kaufman[3] has shown that even brief contact of a pseudophakos to the corneal endothelium can cause endothelial damage because of the removal of cells. An air bubble is frequently instilled into the anterior chamber in cataract surgery, and it has been suggested that intraocular lenses be inserted under an air bubble to protect the endothelium.[4] We have adapted this technique of anterior chamber air instillation in an open system to vitrectomy (a closed endosurgical proce-

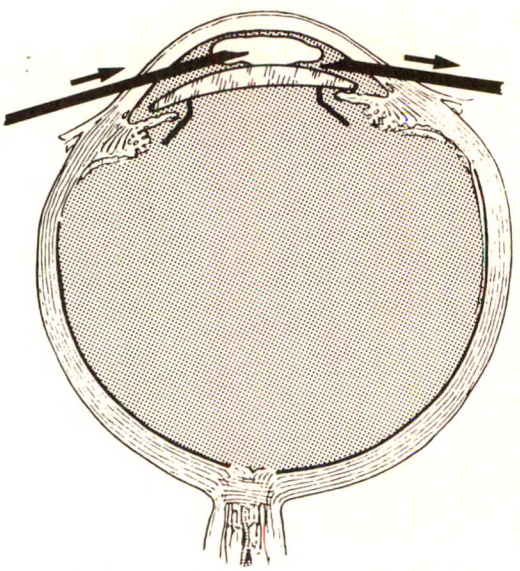

Fig. 2 (Diddie and Smith). A bubble of gas is instilled into the anterior chamber through one needle, while aqueous fluid is passively displaced through a second needle.

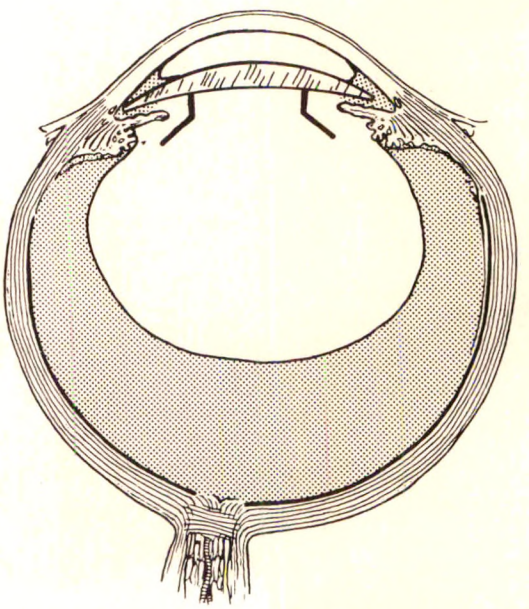

Fig. 3 (Diddie and Smith). With the anterior chamber gas bubble in place, a vitreous cavity gas bubble does not cause endothelial touch with the pseudophakos.

dure), when a pseudophakos is in place. The endothelium is protected by gas. Injection of SF_6 gas into the anterior chamber in rabbits produced transient changes in the corneal endothelium but these changes were not permanent, even on electron microscopy.[5] Preliminary studies in owl monkeys have not shown a toxic effect.

The type of intraocular lens present should be taken into account. We have not had problems of corneal touch after gas injection with Choyce anterior chamber lenses, and thus we have not used this technique in such cases. In patients with iridocapsular-fixated lenses, we have used our technique successfully in two patients. In patients with iris-fixated lenses, a larger gas bubble is required in the anterior chamber to prevent the bubble from slipping between the pseudophakos and the iris into the posterior chamber. However, we have found that a large enough bubble remains in the first critical days to provide the necessary protection.

The concentration of gas is important and should be similar in anterior and posterior chambers. This should minimize the relative movement of gas between chambers. With an intraocular lens in place, a corneal contact lens is needed to perform internal fluid-gas exchange under direct visualization.[6] With the bubble of gas present in the anterior chamber, visualization is reduced, and is sometimes not adequate to perform simultaneous internal fluid-gas exchange. We recommend that with an intraocular lens in place, sequential fluid-gas exchange can be done after instillation of the anterior chamber gas bubble. Not more than 1.5 ml of 100% SF_6 gas should be placed in the vitreous cavity, because that will expand to about twice its volume in 48 hours.[2] The most rapid phase of gas bubble expansion occurs during the first six hours.[7] Intraocular pressure can be increased during this period if too large a volume is placed in either the anterior chamber or vitreous cavity.

Postoperatively, visualization of the fundus is more difficult with this anterior chamber bubble in place. However, gross retinal details can be seen. The benefits of protecting the cornea during surgery seem to outweigh any temporary decrease in visualization of the fundus.

Summary

Two patients underwent vitrectomy with the use of intraocular gas. In one patient the cornea decompensated because of lens-cornea contact and in the second patient a surgical technique devised to protect the cornea from lens contact was used successfully. The technique consisted of injecting a smaller gas bubble into the anterior chamber before the instillation of the posterior chamber gas.

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SCLERAL BUCKLING WITHOUT THERMAL ADHESION

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The primary objective of scleral buckling surgery is the repair of retinal detachment by operative techniques that close retinal breaks and facilitate retinal reapposition. Production of an inflammatory chorioretinal lesion by diathermy or cryotherapy[1] is widely accepted with the resultant scar presumably effecting a tighter than normal bond between neurosensory retina and the retinal pigment epithelium and choroid. We had frequently observed a tenuous relationship between the ophthalmoscopic pigmentary reaction of diathermy or cryotherapy overlying the scleral buckle and the final anatomic result. In some instances the retina remained permanently attached when little or no pigmentary reaction was visible; while in other cases, well treated areas, that is, those with a "leopard-skin" appearance after diathermy or a "salt and pepper" reaction after cryotherapy, subsequently redetached. Zauberman and DeGuillebon[2] described the adhesion characteristics of treated and untreated retina and in 1975[3] reported a series of 37 consecutive cases of repair of retinal detachment without inducing a chorioretinal adhesion, concluding that except for aphakic detachments, buckling procedures to counteract the vitreous traction were sufficient for successful treatment of most groups of retinal detachment.

We examined further the omission of thermal adhesion in scleral buckling surgery on the final anatomic result, and determined whether this approach reduces the incidence of postoperative periretinal proliferation.

MATERIAL AND METHODS

One hundred seventy-five consecutive and unselected cases of retinal detachment were surgically repaired by scleral buckling without thermal adhesion. The group included male and female patients ages 8 to 78 years. One hundred fifty-six of these were primary rhegmatogenous, and two were tractional retinal detachments (Table 1). Seventeen eyes had been operated on six or more months previously, for retinal breaks or detachment or vitreous opacities (Table 2). Selected preoperative characteristics believed to have prognostic significance are summarized in Table 3. Technical variations of the scleral buckling procedures are listed in Table 4.

RESULTS

Initial success, defined as anatomic reattachment for six months after one operation, was achieved in 143 cases or 82% (Table 5). Redetachments occurred in 32 cases or 18%. Of these, six were judged inoperable because of massive

TABLE 1

PATIENTS WITH RETINAL DETACHMENT TREATED BY SCLERAL BUCKLING WITHOUT THERMAL ADHESION

Type of Detachment	No. of Eyes
Primary rhegmatogenous	156
Tractional	2
Previous retinal/vitreous surgery	17
Total	175

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TABLE 2

PATIENTS WITH PREVIOUS RETINAL OR VITREOUS SURGERY*

Type of Surgery	No. of Eyes
SB with cryotherapy	7
SB with diathermy	3
Vitrectomy with SB and cryotherapy	2
Vitrectomy	2
Cryotherapy	2
Laser photocoagulation	1
Total	17

*SB designates scleral buckling.

TABLE 3

SELECTED PREOPERATIVE FINDINGS

Preoperative Findings	No. of Eyes	% of Cases
Periretinal membranes		
Circular fold	40	23
Star fold		
rolled posterior edge,		
or periretinal proliferation	36	20
Hazy media	28	16
Aphakia	81	46
Giant tear	4	2
Duration of detachment		
greater than		
one month	24	14

periretinal proliferation. Twenty-six were reoperated, again by scleral buckling procedures that omitted a chorioretinal thermal adhesion; 11 of these subsequently redetached and were considered as final failures. Causes of initial failure were buckle malposition, periretinal proliferation, new or missed breaks, and inability to close giant breaks (Table 6). Causes of final failure were massive periretinal proliferation in 15 cases, and localized periretinal proliferation in two cases. The incidence of untreatable periretinal proliferation in this series was 10% (17), and it was this group that accounted for the final failures. Table 7 shows the anticipated disparity between a final success rate of 96% (131) in uncomplicated retinal detachments and 68% (44) final success rate in complicated retinal detachments.

TABLE 4

DESCRIPTION OF SCLERAL BUCKLING PROCEDURE*

Operative Detail	No. of Eyes
SB with solid silicone and band	153
SB with silicone sponge and band	19
SB with silicone sponge, no band	3
Revision of SB (re-operations)	26
Subretinal fluid drained	170
Intravitreous air	104
Scleral dissection with implant	166
Silicone explant	9

*SB designates scleral buckling.

DISCUSSION

This study represents the third and largest series of retinal detachments repaired by scleral buckling without thermal adhesion. Zauberman and Rosell[3] treated, similarly, 37 unselected patients including 20 primary rhegmatogenous detachments, three traction detachments, 11 aphakic detachments, and three redetachments previously treated with cryotherapy, diathermy, or local scleral buckling. One of the traction detachments and six aphakic detachments were subsequently reoperated with scleral buckling and cryotherapy but none were successfully reattached.

Chignell[4] reported a series of 29 selected cases of retinal detachment treated by scleral buckling and drainage of

TABLE 5

ANATOMIC RESULTS OF SURGERY

No of Cases	Initial Success	Final Success	Final Failure
175	143 Cases 82%	158 Cases 90%	17 Cases 10%

TABLE 6

CAUSES OF FAILURE

Reason for Initial Failure	No. of Cases	Reason for Final Failure	No. of Cases
Buckle malposition	12	Periretinal proliferation	
Periretinal proliferation	12	Localized*	2
New or missed breaks	5	Massive	15
Inability to close giant breaks	3	Total	17
Total	32		

*Involvement of two quadrants or less.
†Involvement of three or more quadrants.

subretinal fluid but without cryotherapy, diathermy, or photocoagulation. Twenty-six were successfully reattached. Failures were attributed to inaccurate placement of the buckle.

The initial failure of 32 cases (18%) in the present series was the result of the following: (1) buckle malposition, (2) periretinal proliferation, (3) new or missed breaks, and (4) inability to close giant breaks (Table 6). With the possible exception of buckle malposition, it is unlikely that the remaining reasons for failure would have been favorably influenced by a chorioretinal scar.

TABLE 7

RELATIONSHIP OF FINAL SUCCESS TO SELECTED PREOPERATIVE FINDINGS

Preoperative Finding	Final Success (%)	No. of Cases
Uncomplicated retinal detachment	96	131
Complicated retinal detachment*	68	44
Periretinal proliferation		
Vitreous hemorrhage		
Giant tear		
Duration of RD† over one month		
Previous surgery	76	17
Aphakia	87	81

*Cases with one or more of the listed complications.
†RD designates retinal detachment.

Periretinal proliferation remains a primary cause of failure even when thermal adhesions are used, and it would be unreasonable to presume that their omission would actually create additional problems related to proliferative complications. With regard to new or missed breaks, the presence of a thermal adhesion would have had no effect, because the unseen or new break would not have been treated unless, inadvertently, as a result of widespread or indiscriminate treatment of normal retina. In the giant tear failures, the retina could not be replaced either intra- or postoperatively, and therefore, because reapposition was never achieved, treatment with any of the thermal modalities would not have altered the anatomic result.

The relationship of thermal chorioretinal lesions to continued or progressive vitreoretinal traction is more complex. Schwartz and Pruett[5] observed recurrent retinal detachments in 14.5% following the removal of infected silicone implants after scleral buckling with thermal adhesions. In these instances, the chorioretinal adhesion was not strong enough to prevent subsequent redetachment. Continued or increased vitreoretinal traction caused the recurrent detachment, and signified a negligible effect of induced chorioretinal scars on advancing vitreoretinal traction.

Benson, Morse, and Nantawan[6] exam-

ined 341 patients with lattice degeneration treated with cryotherapy, noting that flap tears originated in and extended through treated areas, again suggesting that treated retina does not necessarily resist ongoing vitreoretinal traction.

The relationship of the retina, vitreoretinal traction, and chorioretinal thermal adhesions is neither clearly, nor completely understood. Retinal traction experiments[7] produced the same cleavage plane between neurosensory retina and pigment epithelium in untreated and treated retina. Zauberman[7] concluded that the induced scar did not result in a stronger than normal chorioretinal adhesion. However, it did resist fluid migration into and through the subretinal space. This could have been a factor in our initial failures from buckle malposition. In those cases, even though the retinal tears were not completely closed on the buckle, the presence of a chorioretinal scar might have prevented the movement of fluid through the tear and into the subretinal space. When the retinal break was adequately closed on the buckle, the retina remained permanently attached unless complicated by a new or missed break, progressive vitreoretinal traction, or periretinal proliferation.

Our final anatomic success of 90% (158) paralleled the 90 to 95% incidence of reattachment generally reported in all cases of retinal detachment. Although histopathologic evidence[8] of experimental and clinical cryoapplications convincingly showed strong adhesions characterized by true cell junctions between pigment epithelium and sensory retina, the clinical experience derived from this study supported a different point of view, namely, successful reattachment after the closure of retinal tears on a scleral buckle, and reapposition of untreated sensory retina and pigment epithelium.

The undefined relationship between thermal lesions and massive periretinal proliferation remains a question of critical importance, for if cause and effect could be determined, diminishing or even eliminating thermal treatment would have to be considered. Machemer and Laqua[9] clearly showed the role of retinal pigment epithelium in the formation of periretinal membranes; and the dispersion of pigment, particularly after cryotherapy, implied a possible pathogenetic association between thermal treatment and proliferative complications. This mechanism becomes increasingly suspect in view of Laqua and Machemer's[10] observation of astrocytic proliferation and starfolds after cryogenic necrosis, and essentially the same cellular response in pigment epithelium and retina after diathermy or photocoagulation.[11-15]

These studies suggested a causal relationship between thermal lesions and periretinal proliferation, but our high incidence of massive periretinal proliferation without thermal treatment did not support this contention, and we concluded, therefore, that thermal lesions do not increase the risk of, or necessarily predispose to, massive periretinal proliferation.

Summary

One hundred seventy-five consecutive and unselected patients with retinal detachment were treated with a scleral buckling procedure without inducing a thermal adhesion. In 143 (82%) of these patients reattachment was successful after one operation. In 32 patients (18%) reattachment was not initially successful. These failures resulted from buckle malposition, periretinal proliferation, new or missed breaks, and the inability to close giant tears. Fifteen of the 32 reattached after subsequent scleral buckling without thermal adhesion. Final success was achieved, therefore, in 158 (90%) of the

original group of 175 cases. We concluded that a chorioretinal scar might have prevented initial failure only in those cases of buckle malposition. The high incidence (17, [10%]) of periretinal proliferation, accounting for all of our final failures, did not concur with or support previous impressions indicating a causal relationship between thermal treatment and proliferative complications.

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THE OUTFLOW PATHWAY IN CONGENITAL GLAUCOMA

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Treatment of primary congenital glaucoma may be difficult because the pathogenesis is not clear. The cause of intraocular hypertension is a decrease in facility of outflow.[1-4] The abnormality that causes the resistance to outflow has not been identified.[1-6]

We studied the histopathologic and morphologic factors of the anterior chamber angle in a 5-month-old infant with congenital glaucoma to determine the cause for the increased resistance to aqueous humor outflow in primary congenital glaucoma.

CASE REPORT

A 5-month-old male infant was brought here for consultation by his parents who noted an increase in the size of the eyelids and a white appearance of the eyes. Two months before consultation the infant apparently had photophobia, epiphora, and pink eyes. General physical examination at consultation showed a eutrophic infant with no systemic abnormalities. Ocular examination done with halothane (Fluothane) general anesthesia showed a corneal diameter of R.E.: 15.5 mm and L.E.: 14.5 mm. Intraocular pressure with the Schiøtz tonometer was 37.2 mm Hg for both eyes. Microscopic examination of the anterior segment showed marked corneal edema; observation of anterior chamber structures was not possible. The patient was treated with acetazolamide (10mg/kg of body weight). Six days later an appreciable decrease of corneal edema allowed observation of the chamber angle. Gonioscopy showed a flat insertion of the iris and mesodermal remnants at the angular area. A goniotomy in one inferior quadrant was performed in both eyes. There was no complication during the operation, and the typical descent of the iris root during goniotomy was evident. A mild hyphema was produced and controlled after air injection. Examination with halothane anesthesia eight weeks later showed a corneal diameter of R.E.: 15.5 mm and L.E.: 14.5 mm. Intraocular pressure with the Schiøtz tonometer was R.E.: 21.8 mm Hg and L.E.: 22.4 mmHg. Microscopic examination of the anterior segment showed Haab's striae and transparent cornea; the iris and pupil area were normal. A trabeculotomy operation was done in both eyes according to the technique described by Dannheim and Harms,[7] in the superior 180 degrees. The following modification in the technique was used: The introduction of the trabeculotomy probe into Schlemm's canal was performed at an independent site for left and right side; this allowed an area of 3 mm between sinusotomies to remain untouched, which was excised en bloc from both eyes with Pierce forceps and Vannas scissors. The operation and postoperative period were unremarkable. Twelve months after the operation the last examination of the infant under general anesthesia was performed. The patient was then 20 months old and both eyes were normotensive. The corneal diameter was R.E.: 14.8 and L.E.: 14.3 mm. Intraocular pressure with Schiøtz tonometry was 12.2 mm Hg in both eyes. Microscopic examination of the anterior segment showed conjunctivae of normal appearance. The corneas were transparent and Haab's striae were apparent; the irides were normal and blue. The lenses were transparent in both eyes. Ophthalmoscopic examination was possible with direct ophthalmoscopy and addition of −20 diopters. The cup:disk ratio was 9:10 in the right eye and 8:10 in the left eye. Gonioscopy in the upper half showed a scleral sulcus in the area of Schlemm's canal. The trabeculectomy area was white in color with minor adhesions of the iris root. In the inferior temporal quadrant of the right eye and the inferior nasal quadrant of the left eye, mesodermal tissue filled the angular area. In the remaining quadrant of both eyes, where goniotomy was performed, the angles were wide open and the iris roots were located more posteriorly.

MATERIAL AND METHODS

The angular specimens obtained during the trabeculotomy-trabeculectomy operation from both eyes were immediately fixed in 2.5% glutaraldehyde in

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0.1M cacodylate buffer, pH 7.4, at 0°C for three hours, then refixed in osmium tetroxide for one hour, dehydrated with ethanol and propylene oxide, and later embedded in Araldite. Light microscopic observation was done in sections stained with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope.

Results

The angular specimens were obtained from both eyes at an approximate IOP of 22 mm Hg. The site of excision had not been previously operated on. Sections of tissue for examination were made perpendicular to Schlemm's canal. Those obtained from the left eye included only part of the trabecular area as observed at the light microscope. Sections of the right angle included Schlemm's canal, trabecular meshwork, scleral spur, ciliary muscle, and angular mesodermal tissue. Ultrathin sections of this eye were prepared for electron microscopic observation.

Light microscopy—The angular specimen included all structures of the outflow tract. Schlemm's canal showed an open lumen, the internal wall had many invaginations. It contained red blood cells in its lumen as well as an adjacent collector channel. The scleral spur was perfectly developed. The ciliary muscle reached its normal attachment at the scleral spur. The trabecular area had the typical arrangement of trabecular beams alternated with spaces. The trabecular spaces were well developed at the internal side of the trabecular meshwork. Open trabecular spaces contained red blood cells. These probably migrated from the anterior chamber during surgery. The trabecular beams were wide meridionally, and increased in thickness. The trabecular core was formed by a wide band of fibrous tissue.

The entire extension of the inner side of the trabecular area was covered by mesodermal tissue also present in the chamber angle. The tissue was directly attached to the trabecular meshwork. A border between the two tissues was not visible (Fig. 1).

Electron microscopy—Mesodermal tissue was formed by fibroblasts, collagen fibrils, and ground substance in a loose arrangement. A boundary between mesodermal tissue and the trabecular meshwork was not evident. Thick collagen bands with an irregular course extended

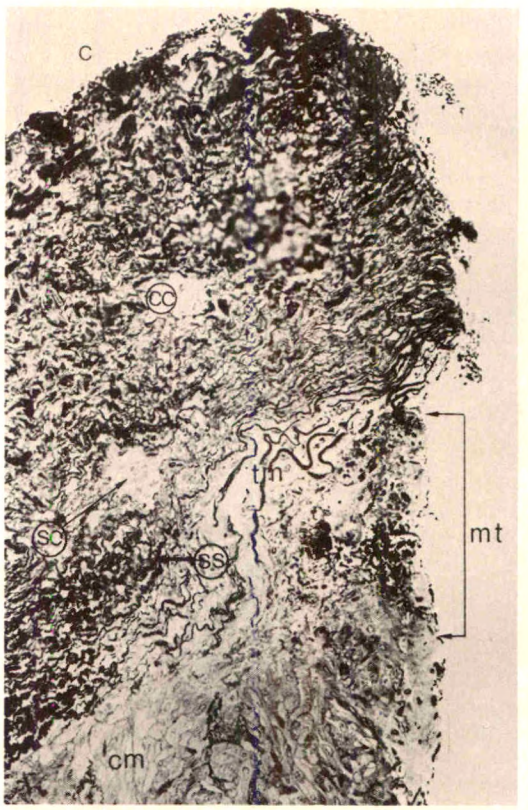

Fig. 1 (Maul and associates). Congenital glaucoma. Light micrograph of outflow pathway. Mesodermal tissue (mt) covers all the extent of trabecular meshwork (tm). Arrangement of trabecular sheets and spaces is present, but there is a thickening of trabecular beams. Internal trabecular spaces show red blood cells. Schlemm's canal appears normal (SC), as well as scleral spur (SS), ciliary muscle (cm), a collector channel (cc) and the cornea (c) (×260).

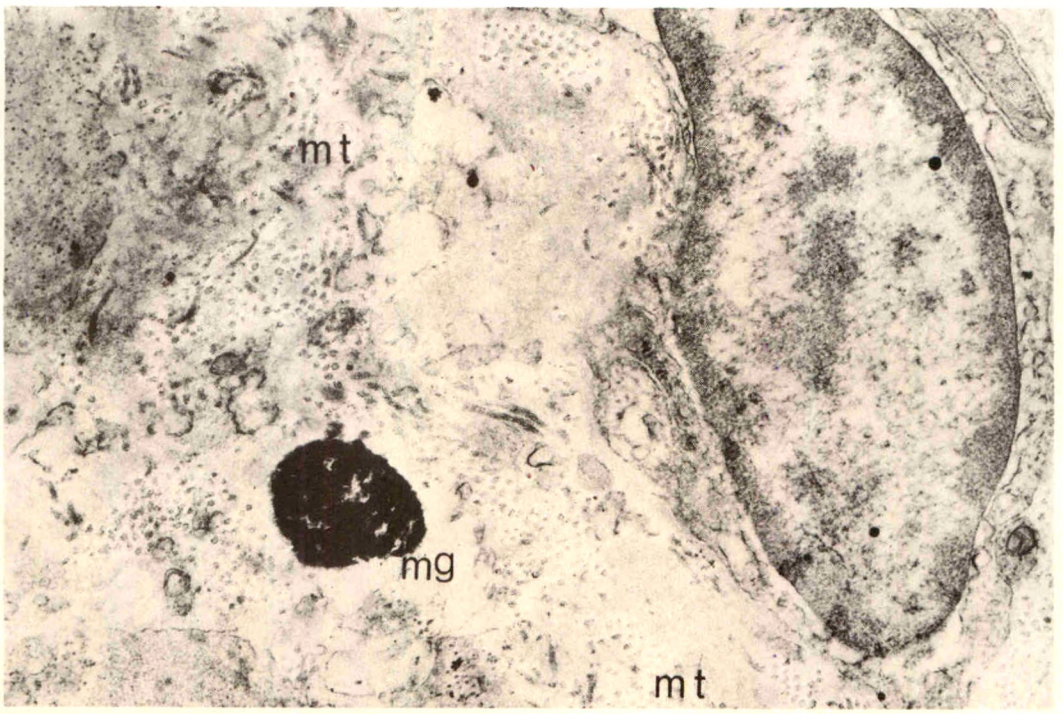

Fig. 2 (Maul and associates). Electron micrograph of chamber angle mesoderm (mt). A loose arrangement of the tissue is evident. Melanin granual (mg) (×17,000).

into the mesodermal tissue from the trabecular side (Figs. 2 and 3).

Trabecular meshwork—This area showed many abnormalities. The most remarkable were thickening of the trabecular beams and fibrosis of the trabecular matrix. Trabecular beams in the internal area were well formed, with an endothelial lining and a trabecular matrix. This was formed by ground substance and abundant collagen fibrils (Fig. 4). In external areas of the trabecular meshwork, trabecular beams were also lined by endothelial cells, but the trabecular core contained abnormal elements. Cells of endothelial type and thick collagen bands were found in the trabecular matrix. The trabecular spaces were well formed in internal areas of the trabecular meshwork that contained red blood cells. In external areas endothelial cells were evident, but there was no adjacent space; thick collagen bands and granular material were found instead (Fig. 5). The collagen bands found in the trabecular core were one of the most constant findings (Fig. 6).

A great amount of collagen fibrils was found in the juxtacanalicular trabecular meshwork. They had multidirectional orientation and were seen in the area underlining the internal wall of Schlemm's canal. There were also endothelial cells between the collagen bundles. This part of the trabecular meshwork was increased in thickness. No red blood cells were observed in this area (Fig. 7).

Schlemm's canal had an open lumen of irregular contour. Its wall was lined by endothelial cells. In only two sections did endothelial cells show giant vesicles facing the lumen. Except for the absence of vesicles, the morphology of endothelial cells was normal (Fig. 8). In the subendothelial area of Schlemm's canal a thick and constant layer of amorphous

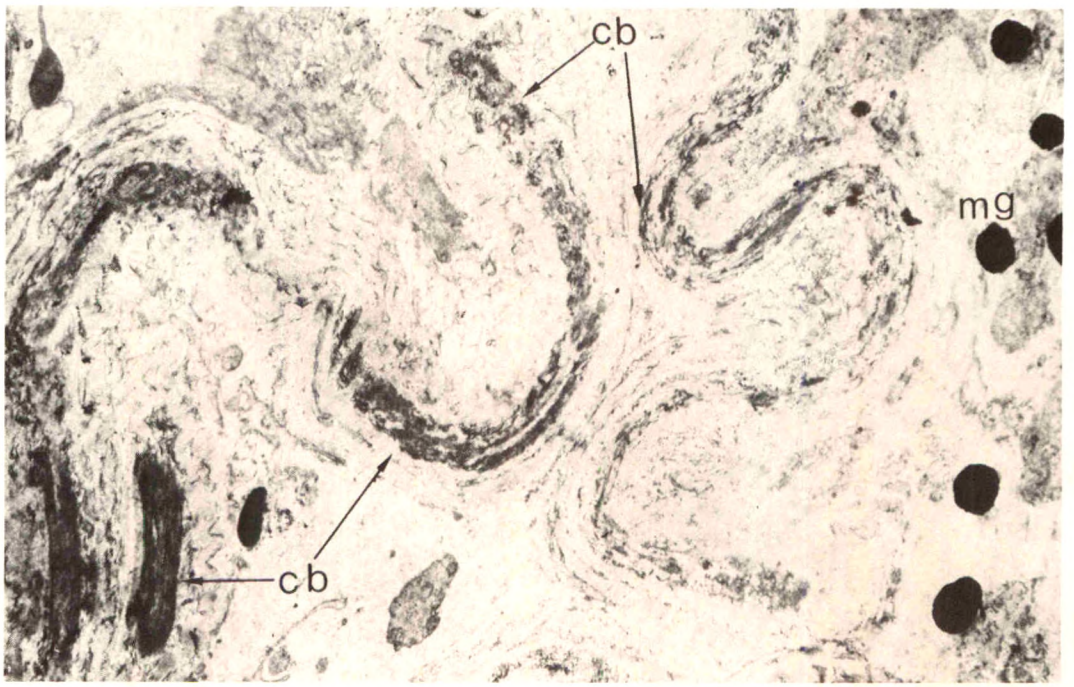

Fig. 3 (Maul and associates). Electron micrograph of mesodermal tissue near trabecular area. Melanin granules are seen (mg). As the tissue approaches the trabecular area collagen bands (cb) reach it with an irregualr course (×8,580).

material was found. This layer was present on the entire internal wall and was found in all sections studied. The lamina was formed by amorphous material adherent to all invaginations of the endothelium. Red blood cells or other cells were not seen in this layer. At high magnification endothelial cells showed zonulae adherentes with adjacent cells and no specific attachment to the underlying abnormal basal layer (Fig. 9).

Discussion

The outflow tract in this case of congenital glaucoma showed abnormalities at three sites. In the internal region mesodermal tissue covered the normally filtrating uveal trabecular meshwork. Trabecular beams were thicker than normal. The trabecular core had an increased amount of collagen that formed bands visible at light microscopy, thus changing the aspect of cellularity of the trabecular meshwork at light microscopy to one of fibrosis. Trabecular spaces were not apparent in external areas. Finally a layer of amorphous material was present in the subendothelial area of Schlemm's canal internal wall. From these findings we believe that the cause for decreased outflow in congenital glaucoma is abnormalities of the trabecular meshwork.

The relation of mesodermal remnants at the angular region to increased resistance to aqueous humor outflow has been discussed.[1-6] Pathogenic study of congenital glaucoma has generally been focused on the area in front of the trabecular meshwork, where the presence of mesodermal remnants has given the anatomic basis for the concept of faulty development of the chamber angle in congenital glaucoma, assuming the trabecular meshowrk in normal in all ways. However, the relationship of the mesodermal tissue itself to increased resistance is not clear. Maumenee[4,8] studied the role of mesodermal remnants in producing in-

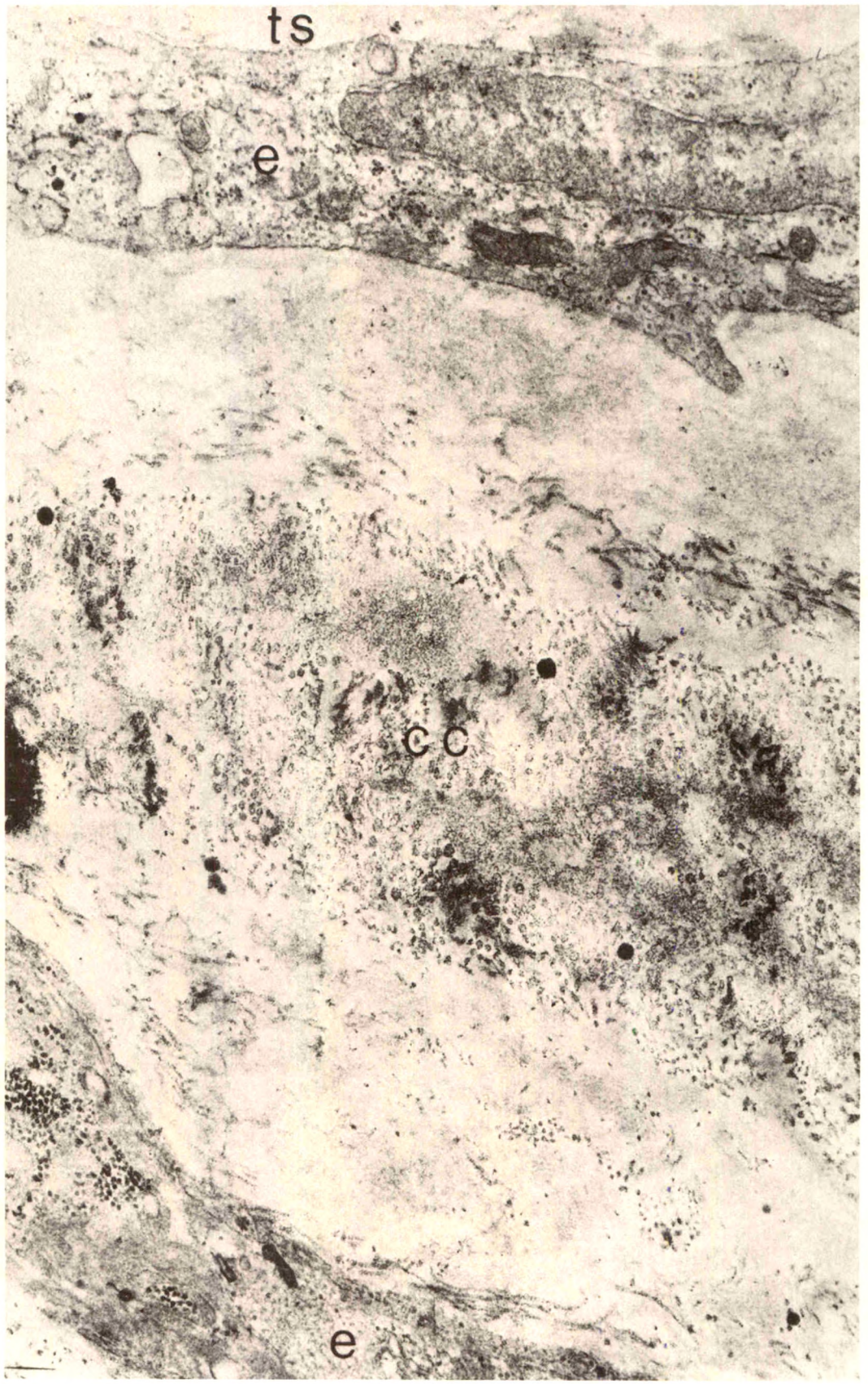

Fig. 4 (Maul and associates). Electron micrograph of trabecular beam in uveal trabecular meshwork. Endothelial lining (e), collagen core (cc), and neighboring trabecular space (ts) are seen (×8,000).

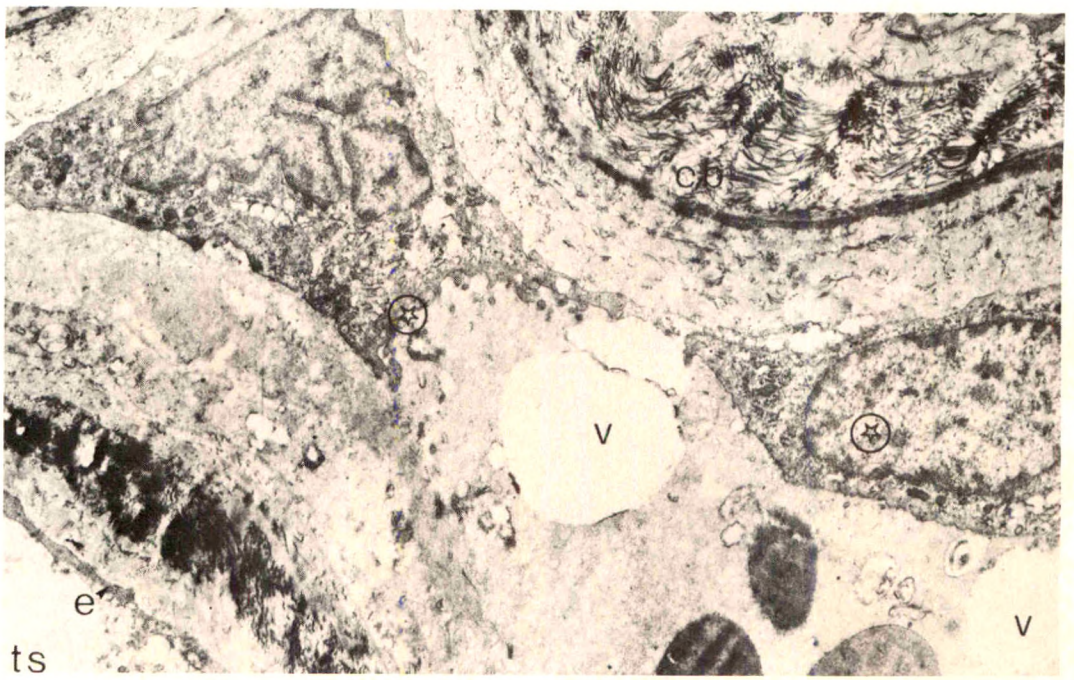

Fig. 5 (Maul and associates). Electron micrograph of corneoscleral trabecular meshwork. Endothelial lining (e) is present in one side of the trabecular beam with neighboring trabecular space (ts). The trabecular matrix contains abnormal elements. Liquid spaces (v), endothelial type cells (asterisk and circle), and thick collagen bands (cb) (×8,000).

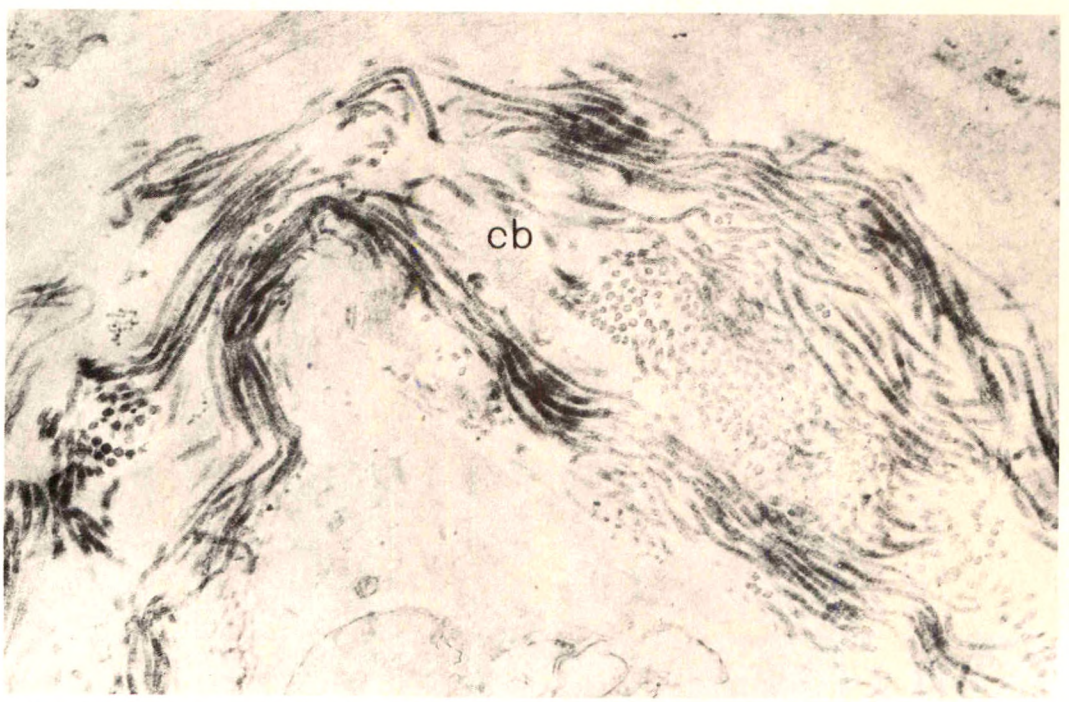

Fig. 6 (Maul and associates). Electron micrograph of collagen bands (cb), which gives the trabecular meshowrk a fibrillar aspect instead of the normal cellular aspect (×25,200).

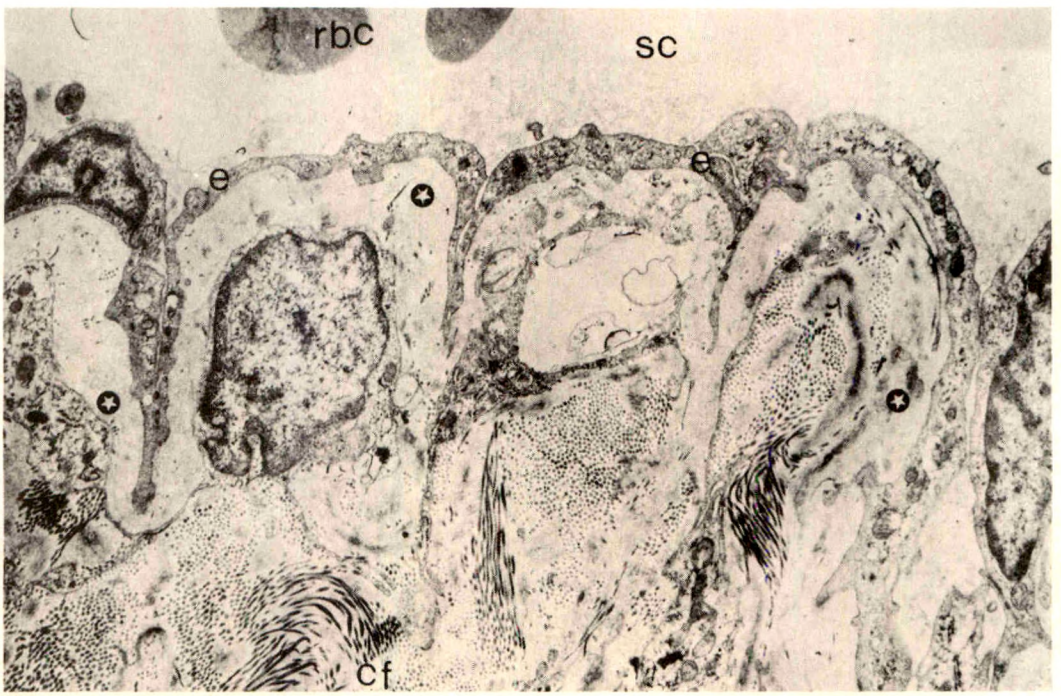

Fig. 7 (Maul and associates). Electron micrograph of juxtacanalicular meshwork and Schlemm's canal. It shows a great amount of collagen fibrils (cf). Schlemm's canal is open (sc) with red blood cells (rbc) in its lumen. Endothelial lining (e) is underlined by a constant layer (asterisk) of amorphous material (×10,500).

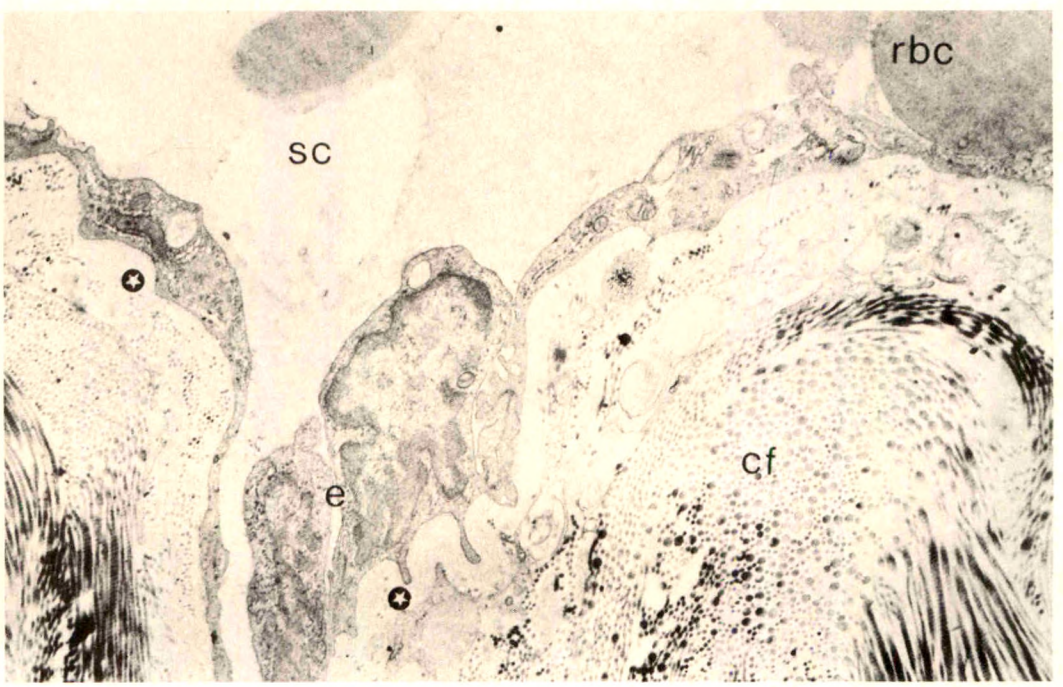

Fig. 8 (Maul and associates). Electron micrograph of internal wall of Schlemm's canal (SC). Endothelial cells (e), subendothelial layer of amorphous material (asterisk), and collagen fibrils (cf) in the juxtacanalicular trabecular meshwork are indicated (×9,500).

Fig. 9 (Maul and associates). Electron micrograph of endothelial cell (e) at inner wall of Schlemm's canal (SC). Thick and constant layer of amorphous material at subendothelial area is shown (asterisk) coriginal magnification, (×33,000).

creased resistance to outflow. In 24 of 29 eyes studied, the trabecular area was partially covered by mesodermal tissue, and in only five cases was the trabecular meshwork completely covered by mesodermal remnants. Many bilateral cases studied had an asymmetrical amount of the trabecular meshwork covered by mesodermal tissue. Worst[2] suggested that the band of angular mesodermal tissue present in congenital glaucoma could not be the site of resistance. For Worst[2a] and Barkan[9] the obstruction site for aqueous flow was an ultrathin membrane covering the angular mesoderm, probably originating in Descemet's membrane. This possibility was raised from clinical observation during goniotomy. We could not show Barkan's membrane in our case. Ocular pathologists (F. Contreras, personal communication, 1978)[8,10] have also not been able to show this membrane in eye specimens. In this study the angular mesoderm appears as a loose tissue with no apparent morphologic barrier mechanism. We believe that this tissue is not the main obstacle to aqueous flow.

The abnormalities found in the trabecular meshwork in this study suggest that it is the site of main resistance to outflow. Maumenee[4,8] was the first to describe trabecular abnormalities in congenital glaucoma. In 21 of 25 cases with congenital glaucoma he found an abnormal insertion of the longitudinal fibers of the ciliary muscle into the trabecular meshwork, in front of the scleral spur. He suggested this finding as the main cause of increased resistance and the most constant abnormality of the angle in this disease.

Analyzing our observations, the more internal zone of trabecular meshwork does not appear to offer resistance to aqueous flow even though it is not perfectly normal. There were red blood cells in the trabecular spaces of this area. Because red blood cells reached this area suggests that aqueous humor may also

have free passage to this area. Remarkable was the absence of spaces in the external areas of the trabecular meshwork, and the presence of increasing amounts of collagen in this area.

The area of the juxtacanalicular trabecular meshwork was also thickened by collagen fibrils. Recently, Anderson[11] also described and discussed abnormalities of the trabecular meshwork in congenital glaucoma.

On the internal wall of Schlemm's canal a layer of amorphous material was found; its nature and meaning are unknown to us. It does not have the appearance of a basal lamina and does not appear to be synthesized by the endothelium. It could represent some form of deposit, a result of obstructed flow.

On the basis of our present observations we believe that the abnormality responsible for increased resistance to outflow was a malformation of the trabecular meshwork. Even though the examination of more cases will be needed, the higher success rate of trabeculotomy in this disease supports our hypothesis.[12-15]

Summary

We obtained specimens from the angle of the eye during a trabeculotomy-trabeculectomy operation of a 5-month-old boy with congenital glaucoma. Light and electron microscopy of the anterior chamber angle showed the presence of mesodermal tissue covering the entire trabecular area. The trabecular meshwork showed thickening of trabecular beams, and an increased amount of collagen fibrils in the trabecular matrix. Internal trabecular spaces contained red blood cells; outer trabecular spaces were not apparent. The juxtacanalicular trabecular meshwork was thicker than in normal cases, because of an increased amount of collagen fibrils. The endothelium of Schlemm's canal was underlined by a thick and constant layer of amorphous material. These observations suggested that the site of increased resistance to aqueous humor outflow in congenital glaucoma could be found in abnormalities of the trabecular meshwork and the internal wall of Schlemm's canal.

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BILATERAL OPTIC ATROPHY CAUSED BY CHRONIC ORAL INGESTION AND TOPICAL APPLICATION OF HEXACHLOROPHENE

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Hexachlorophene has been shown to be a neurotoxic agent in laboratory animals and in children. We report a case of optic atrophy in a 31-year-old woman, which was probably caused by chronic hexachlorophene ingestion.

CASE REPORT

In March 1975, a 31-year-old woman with visual loss was referred here. She and her family had no history of ocular problems. At age 29 years she had a "spell" of bilateral blindness with right-sided numbness and weakness lasting about five minutes with complete resolution and no recurrences. She underwent surgery in March 1974 to remove a growth from her right ear. After this, she began taking an estimated 10 to 15 ml of hexachlorophene (pHisoHex) orally daily during the next ten to 11 months. She also applied large amounts of hexachlorophene to her face every day as self-treatment for pimples. She was depressed during this time. She noted no headache, diplopia or dizziness, but may have had intermittent numbness of her left foot.

In January 1975 she noted decreasing vision, first in her right eye, described as a superior visual field loss that progressed inferiorly. She saw a physician several days later. By that time her visual acuity was poor in the right eye and also abnormal in the left eye. She was told that she had optic atrophy and was referred to us for further examination. She was taking no medications with the exception of the hexachlorophene. She reported no exposure to chemicals other than hexachlorophene.

Ophthalmic examination revealed a visual acuity of R.E.: hand motions and L.E.: 6/90 (20/300). Both pupils were round and 6 mm in diameter. The left pupil reacted more rapidly to light than the right pupil, and there was no afferent pupillary defect on the right. The near response was normal in both eyes. The patient could not detect the isochromatic color plates with her right eye; with the left eye she could identify only the demonstration plate. There was an intermittent exotropia, but both versions and ductions were full. Fine upbeat nystagmus was present on upgaze. The optokinetic response was normal in the left eye, but she could not see the tape with the right eye.

Slit-lamp examination and intraocular pressures by applanation were normal. Ophthalmoscopic examination showed severe bilateral optic atrophy, which was worse in the right eye than in the left eye. Nerve fiber layer thinning was evident, but no other retinal abnormalities were noted. Visual fields showed a small irregular island of vision near, but not including, fixation in the right eye and a superotemporal quadrantanopia in the left eye (Fig. 1). Electroretinography and visual-evoked response testing were not done. The patient was admitted to the hospital for examination of a possible intracranial tumor.

During her hospitalization, a hypochromic, microcytic, iron deficiency anemia was uncovered. Electrolytes, blood urea nitrogen, creatinine, and liver enzymes were normal. Lumbar puncture was normal with cerebrospinal fluid and serum serology nonreactive. Chest x-ray, plain skull films, views of the optic foramina and computed axial tomography scan with and without contrast were all normal. A pneumoencephalogram showed thickening and widening of the optic chiasm (Fig. 2).

The psychiatric consultant found hypochondriacal obsessions, perhaps delusions and occasional depression, but she was not thought to be schizophrenic. Once or twice during her hospital stay, the patient ingested hexachlorophene despite repeated advice not to do so.

She was discharged with a diagnosis of hexachlorophene-induced optic atrophy and followed up as an outpatient. During subsequent visits to our office, the appearance of the fundus was not changed. Her visual fields improved and eventually stabilized (Fig. 3). Visual acuities also improved and stabilized. Four months after discharge visual acuity was R.E.: 6/120 (20/400) and L.E.: 6/12 (20/40). Fourteen months after discharge, visual acuity was R.E.: 6/120 (20/400) and L.E.: 6/7.5 (20/25) with no subsequent changes.

DISCUSSION

Hexachlorophene is an effective antistaphylococcal germicide used as soap or detergent in a 2% (w/w) concentration. After oral or topical administration, neurotoxicity has been shown in animals such as rats,[1,2] calves, sheep,[3] monkeys,[4]

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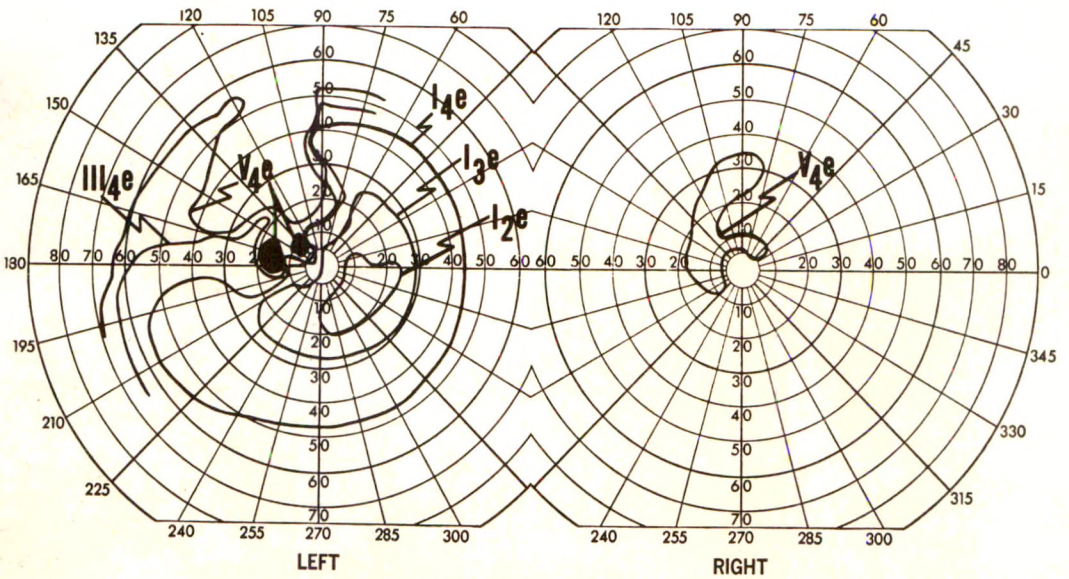

Fig. 1 (Slamovits, Burde, and Klingele). Visual fields obtained shortly after initial examination show a small irregular island of vision near, but not including, fixation in the right eye and a superotemporal quadrantanopia in the left eye.

and tadpoles.[5] Human neurotoxicity has been reported also after percutaneous application of hexachlorophene in premature infants, full-term babies with normal skin,[6] patients with burns[7,8] or ichthyosis, as well as after ingestion.[8-10]

Typical autopsy findings in both animals[1,2,5] and humans[6,9,11] include brain edema and myelin loss and vacuolation[1] (synonyms include honeycombing[6] or vacuolization[9] or "aspec de dentelle"[11]) of the myelin sheath. A number of these studies stress the extensive involvement and particular susceptibility of the optic nerve and chiasm in both animals[1-3,7] and humans.[6,9]

Towfighi, Gonatas, and McCree[1] reported hind leg weakness or paralysis after oral administration of hexachlorophene to young adult rats. Findings

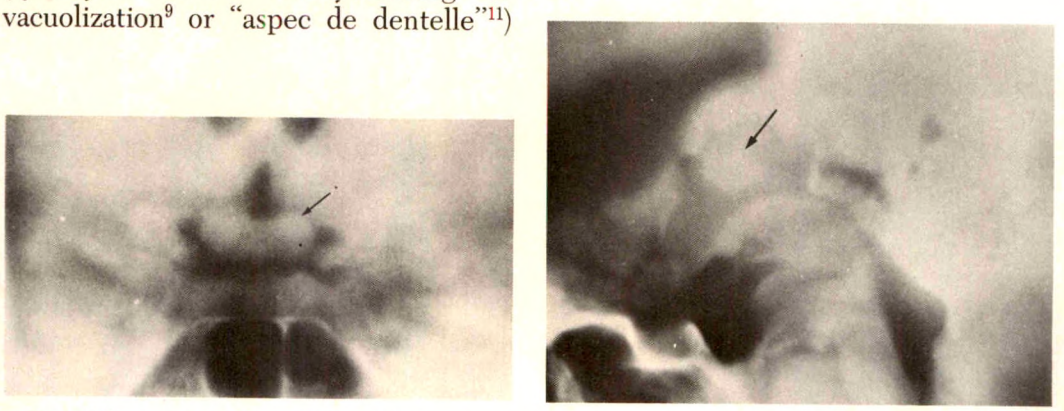

Fig. 2 (Slamovits, Burde, and Klingele). Suprasellar pneumopolytomography. Left, Frontal section shows a symmetrically widened and thickened chiasm (arrow), 24 × 9 mm in maximum dimensions (upper limits of normal being about 19 × 7 mm). Right, Lateral view again shows the enlarged chiasm (arrow). The sella turcica is normal.

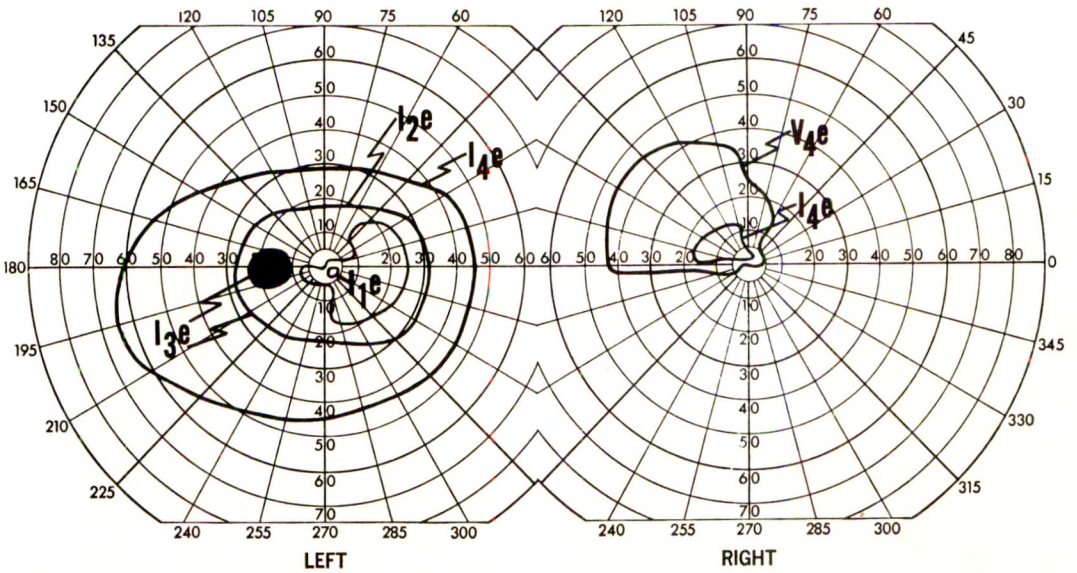

Fig. 3 (Slamovits, Burde, and Klingele). Visual fields obtained 28 months after initial examination showing improvement (compare to Figure 1).

included vacuolation of myelinated fibers in the central nervous system and peripheral nerves, which was more evident in large than small fibers. Similarly, more vacuolation was found in central than in peripheral nerve myelin with the most severe changes seen in the optic nerve. They described cerebral and cerebellar white matter softness and swelling as well as enlargement throughout the entire course of the optic nerves.

In rats given a diet containing hexachlorophene, Rose, Wisniewski, and Cammer[2] described intraperiod splitting of myelin, which was visible on electron microscopy. In one report[12] the rat retina was studied after a hexachlorophene diet. Disruption of the disk membranes of the rod outer segments was noted together with photoreceptor loss. Towfighi, Gonatas, and McCree[12] postulated the same mechanism for photoreceptor disk and intramyelinic vacuolation, that is, hexachlorophene affinity for extracellular components of both receptor lamellae and myelin.

Goutières and Aicardi[6] described autopsy findings after percutaneous hexachlorophene intoxication of children with normal skin. Optic nerves and spinal cord were described as swollen, and massive cystic spongiosis of the white matter of the hemispheres was noted. They stated: "Oedema was most pronounced in the U fibres, internal capsule, white fasciculi coursing through the basal ganglia and optic nerves." At autopsy of a boy who had died after accidental oral hexachlorophene ingestion, Martinez, Boehm, and Hadfield[9] found diffuse white matter vacuolization and a selective optic pathway necrosis anterior to the geniculate bodies.

The present case lends further clinical support to laboratory observations. Our patient had significant visual impairment caused by anterior visual system damage. Possibly the apparent improvement in visual fields and visual acuity represents subsidence of optic nerve edema after discontinuation of hexachlorophene use. The present stable visual acuity and visual fields probably reflect the true extent of the optic nerve damage induced

by hexachlorophene. Clinical evaluation showed bilateral optic neuropathy, and pneumoencephalography showed an enlarged chiasm. Results of neurologic examination were normal except for the optic atrophy. The patient denied symptoms of gastrointestinal disease, although an iron-deficiency anemia was found. Laboratory studies disclosed no other abnormalities.

Our patient, by conservative estimate, consumed an estimated 10 to 15 ml of hexachlorophene daily during a period of approximately ten months, in addition to frequent skin application. Some ingestion took place in the hospital, despite warnings not to take it. What oral doses are likely to cause toxicity is unclear from published reports. For example, Martinez, Boehm, and Hadfield[9] reported the death of a 7-year-old boy after a 45-ml dose was taken orally. Henry and DiMaio's[10] patient, a 46-year-old woman, died after taking 200 ml of hexachlorophene orally. Lustig's[13] patient, a 6-year-old, died after drinking 4 to 5 ounces of hexachlorophene; yet, an infant who had a "spoonful" of hexachlorophene with each feeding for several days had no residual effects.[14]

It appears that adults tolerate greater doses than children, and susceptibility is variable. Our case shows that anterior visual system damage can be present when no other signs of poisoning are present.

Summary

A 31-year-old woman ingested hexachlorophene (pHisoHex) over a ten-month period. She developed bilateral optic atrophy with no other systemic evidence of neurotoxicity. This case supports pathologists' findings that the optic nerve and chiasm are particularly sensitive to the poisonous effects of hexachlorophene.

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ADULT-ONSET FOVEOMACULAR PIGMENT EPITHELIAL DYSTROPHY

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We describe an adult-onset macular dystrophy that ophthalmoscopically resembles Best's dominant vitelliform dystrophy. The macular lesion is small, slightly elevated, yellow, and subretinal. Hyperpigmentation occurs either within or around the lesion. The condition occurs in association with a mild to moderate decrease in vision, a characteristic ring of hyperfluorescence that surrounds an area of hypofluorescence on fluorescein angiography, and a normal or slightly subnormal electro-oculogram (EOG) in most cases. These findings are based on 33 cases.

SUBJECTS AND METHODS

Thirty-three patient records were reviewed from the files of one of us (H.S.). All patients had a complete ocular examination and fundus photographs. Thirty-two patients had fluorescein angiography and 20 patients had EOGs. Some patients had additional studies performed when indicated. We report those cases that showed the nature of the macular disease or that showed unusual associated features.

CASE REPORTS

Case 13—A 48-year-old white woman complained of a gradual bilateral decrease in vision for four years. Her medical history was unremarkable. On initial examination, visual acuity was 6/12 (20/40) in each eye. A round, yellow, subretinal, 500-μ lesion with surrounding pigment clumps was present in each fovea (Fig. 1, top). In the periphery of each retina there was a band of pigmentary disturbance that had a "bone spicule" appearance (Fig. 1, middle left). Fluorescein angiography showed a ring of hyperfluorescence surrounding each fovea (Fig. 1, middle right, bottom left). An EOG showed a definitely abnormal light/dark ratio of 1.4 for the left eye and a slightly subnormal value of 1.6 for the right eye. The photopic electroretinogram was normal in both eyes. The scotopic responses were normal in wave form but were reduced to less than one half of the normal amplitude bilaterally. Nine months later, visual acuity had deteriorated to R.E.: 6/21 (20/70) and L.E.: 6/15 (20/50). The yellow subretinal material of the right fovea had decreased in size (Fig. 2, left). Fluorescein angiography of the right macula showed a more prominent central hypofluorescence with a surrounding ring of hyperfluorescence (Fig. 2, right). The patient's four children had no visual complaints.

Comment—This patient showed evidence of two diseases: a central maculopathy and a peripheral pigmentary degeneration. Although the yellow lesion of the right macula decreased in size with time, the area of central hypofluorescence on angiography increased with a more prominent ring of hyperfluorescence.

Case 15—A 57-year-old white man was examined for decreased vision in the left eye that had continued for three months. His medical history was noncontributory. Visual acuity was R.E.: 6/9 (20/30) and L.E.: 6/60 (20/200). A yellow, subretinal, 500-μ lesion with central pigment clumps was present in the right fovea (Fig. 3, top left). The left fovea showed a yellow, 750-μ lesion with peripheral pigment clumps that was surrounded by fresh subretinal hemorrhage (Fig. 3, top right). Fluorescein angiography showed hypofluorescence of the right fovea surrounded by a subtle ring of hyperfluorescence (Fig. 3, bottom left). In the left macula, there was extensive hypofluorescence caused by the hemorrhage. There was also a central area of lacy hyperfluorescence that enlarged during the angiogram, suggesting subretinal neovascularization (Fig. 3, bottom right). An EOG showed normal responses with a light/dark ratio of 1.8 for the right eye and 2.0 for the left eye. The patient's mother and brother were examined by their ophthalmologists and no macular abnormality was found.

Seventeen months later, the patient's visual acuity was R.E.: 6/15 (20/50) and L.E.: 6/60 (20/200). Examination showed an inferior branch vein occlusion in the right eye and enlargement of the subreti-

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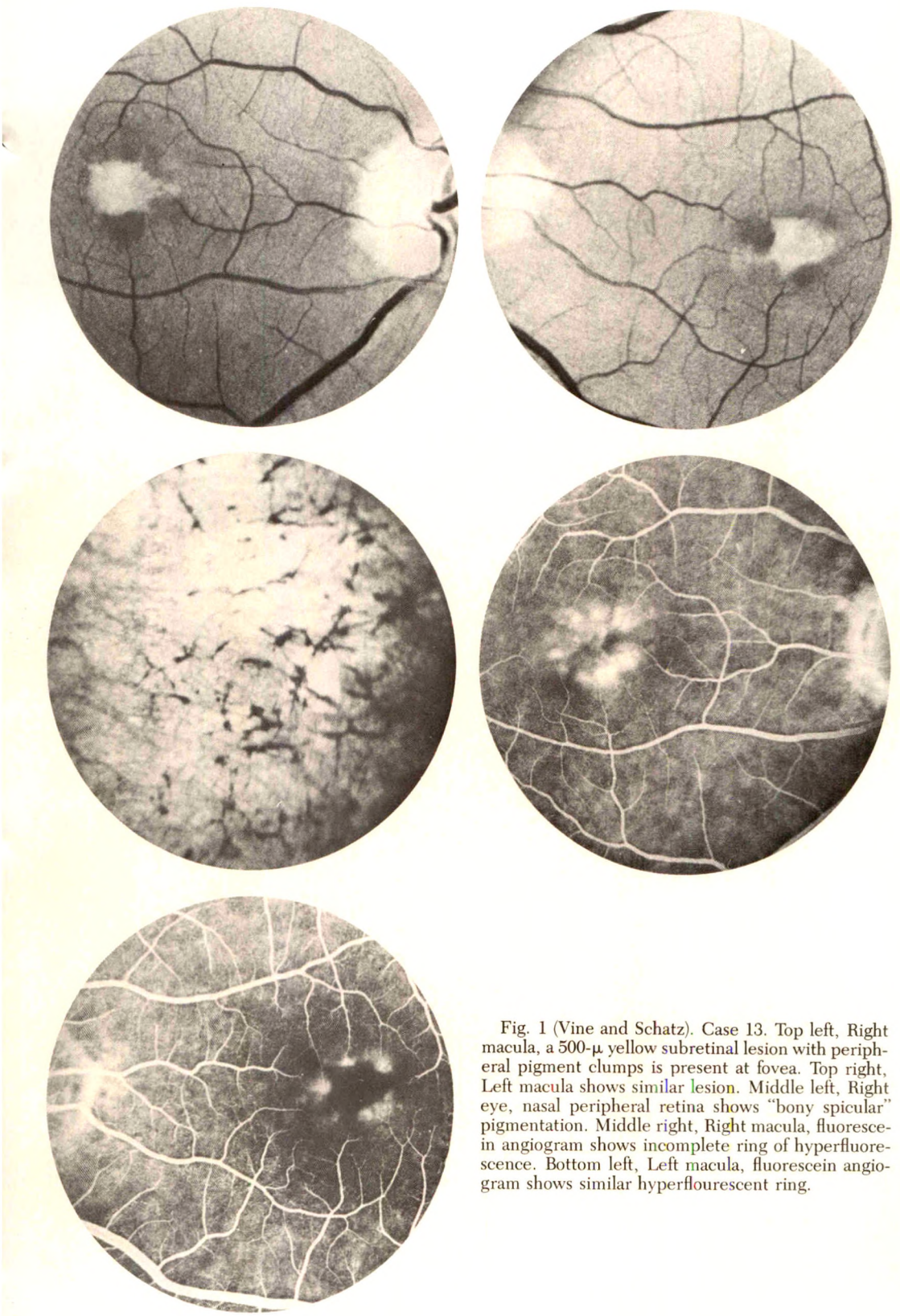

Fig. 1 (Vine and Schatz). Case 13. Top left, Right macula, a 500-μ yellow subretinal lesion with peripheral pigment clumps is present at fovea. Top right, Left macula shows similar lesion. Middle left, Right eye, nasal peripheral retina shows "bony spicular" pigmentation. Middle right, Right macula, fluorescein angiogram shows incomplete ring of hyperfluorescence. Bottom left, Left macula, fluorescein angiogram shows similar hyperflourescent ring.

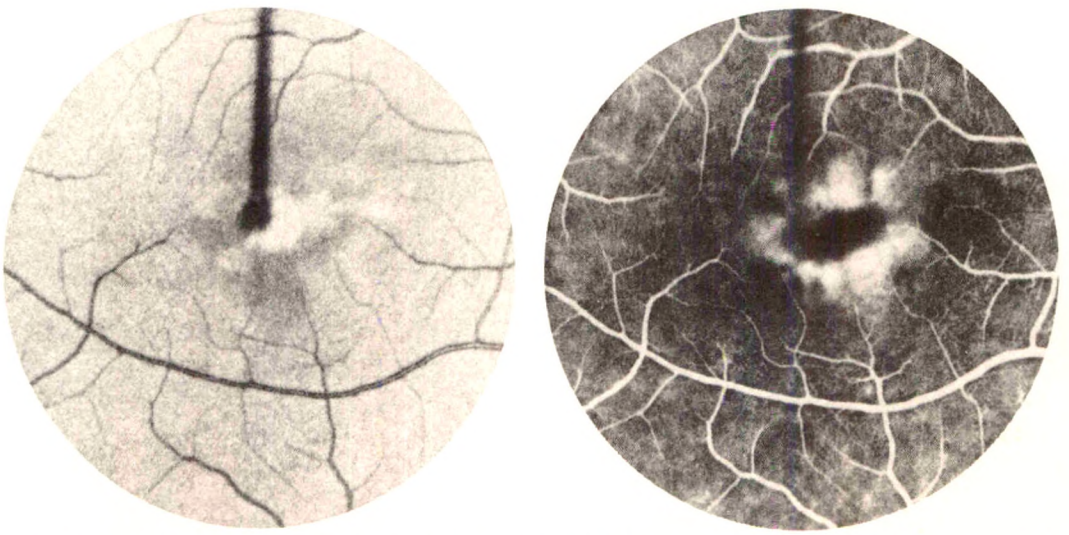

Fig. 2 (Vine and Schatz). Case 13. Nine months later. Left, Right macula, yellow foveal lesion has decreased in size. Right, Right macula, fluorescein angiogram shows ring of hyperfluorescence is more prominent with larger hypofluorescent center.

nal hemorrhage in the left macula. The patient returned a few months later with a visual acuity of R.E.: 6/21 (20/70) and L.E.: 6/60 (20/200). A small inferior foveal hemorrhage was present in the right eye (Fig. 4, left). Fluorescein angiography showed a small subretinal neovascular net in the right fovea (Fig. 4, right). During two subsequent follow-up examinations, visual acuity was R.E.: 6/15 (20/50) and L.E.: 6/60 (20/200). Despite the improved vision, fluorescein angiography showed enlargement of the subretinal neovascular net in both eyes.

Comment—This man was one of two patients in our series who developed subretinal neovascularization associated with this pigment epithelial dystrophy.

Case 18—A 50-year-old white woman complained of bilateral metamorphopsia for 11 years and decreased vision in the right eye for one year. Her medical history was noncontributory. Visual acuity was R.E.: 6/21 (20/70) and L.E.: 6/6 (20/20). Each fovea contained a yellow, subretinal lesion with dark pigment clumps around the periphery of the lesion (Fig. 5, top). Fluorescein angiography of the left macula showed a central area of foveal hypofluorescence surrounded by a ring of hyperfluorescence (Fig. 5, bottom left). The right macula showed no abnormal hyperfluorescence (Fig. 5, bottom right). Thirteen months later, the visual acuity was R.E.: 6/30 (20/100) and L.E.: 6/9 (20/30). The EOG showed normal responses of 1.9 for each eye. The patient's mother (Case 17) showed bilateral yellow subretinal lesions and moderate visual loss. The patient had no siblings.

Case 28—A 37-year-old white woman complained of metamorphopsia in each eye that lasted eight months. She had been treated for asthma with various medications for most of her life. Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/9 (20/30). Two yellow parafoveal adjacent accumulations of subretinal material with pigment clumps were present in each macula (Fig. 6, top). Fluorescein angiography showed two rings of hyperfluorescence in each macula (Fig. 6, bottom). The EOG was R.E.: 1.65 and L.E.: 1.70.

Comment—This woman was one of two patients who showed two subretinal yellow accumulations within the same macula. The right eye in Case 25 had one foveal lesion and a smaller perifoveal satellite lesion. Each of these separate lesions showed the characteristic ring of hyperfluorescence on fluorescein angiography.

Results

Each of the 33 patients in our series showed a characteristic foveal or parafoveal lesion that was round, yellow, and subretinal with associated central or surrounding black pigment, or both. The macular lesions had other identifying characteristics as well: the diameters ranged from 250 to 750 μ with a mean of

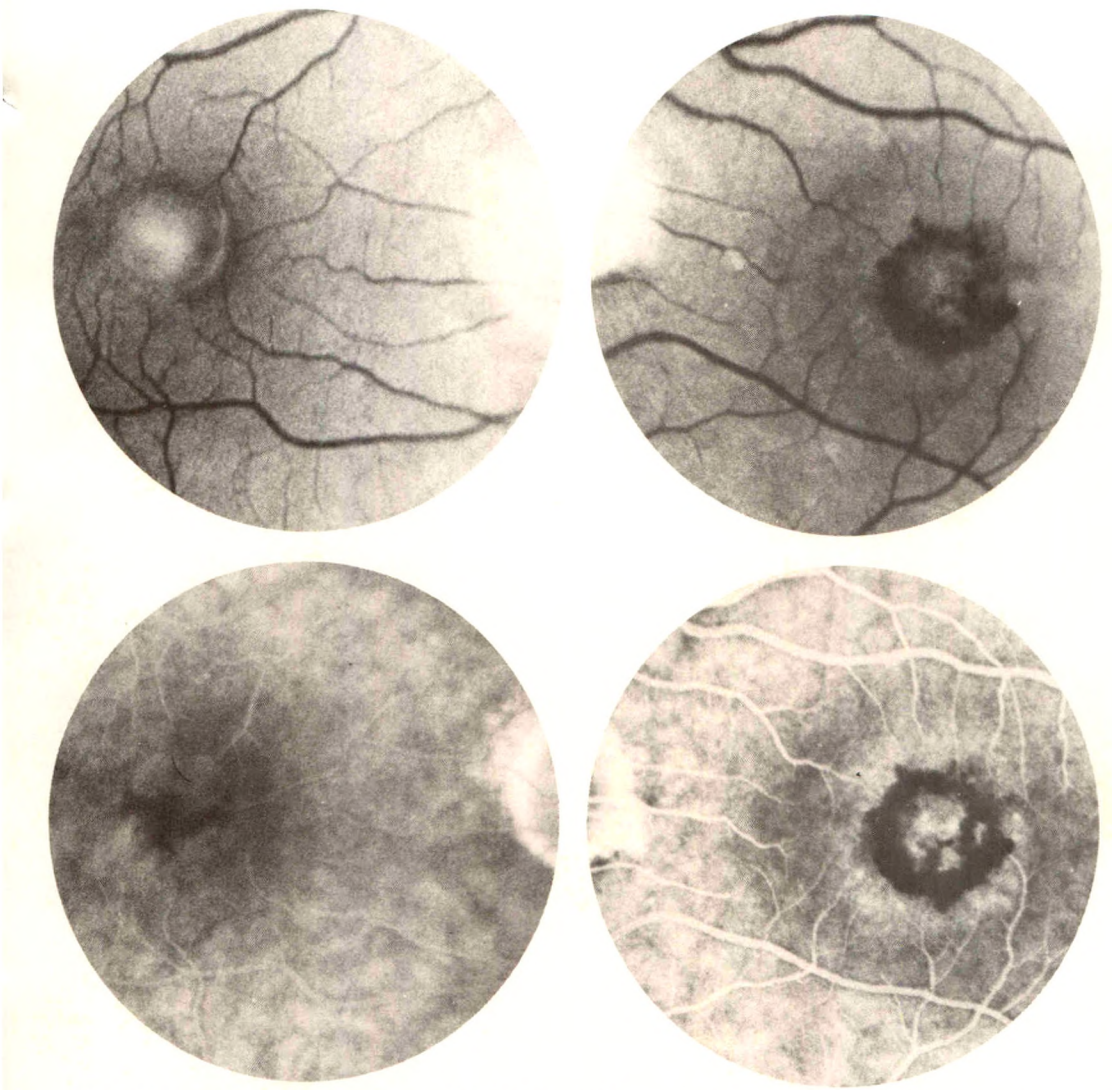

Fig. 3 (Vine and Schatz). Case 15. Top left, Right macula, A 500-μ yellow elevated subretinal foveal lesion Top right, Left macula, central yellow macular lesion surrounded by subretinal homorrhage. Bottom left, Right macula, fluorescein angiogram. A faint, hyperfluorescent ring surrounds a central hypofluorescent area in fovea. Bottom right, Left macula, fluorescein angiogram. Circular area of hypofluorescence caused by blockage from hemorrhage and central lacy hyperfluorescence caused by subretinal neovascularization.

500 μ; there was a ring of hyperfluorescence surrounding an area of hypofluorescence on fluorescein angiography; and the associated EOGs. were generally normal or slightly subnormal. Twenty-five of the 33 patients had bilateral lesions. All patients were adults ranging in age from 37 to 80 years with a mean age of 62 years. One patient was black and the rest were white. Eighteen patients were women and 15 were men. There was no apparent relationship between the presence of the macular lesion and any systemic illness or medication (Table 1).

The visual acuities of the 58 eyes that showed the maculopathy are shown in Table 2. In most patients, the vision of

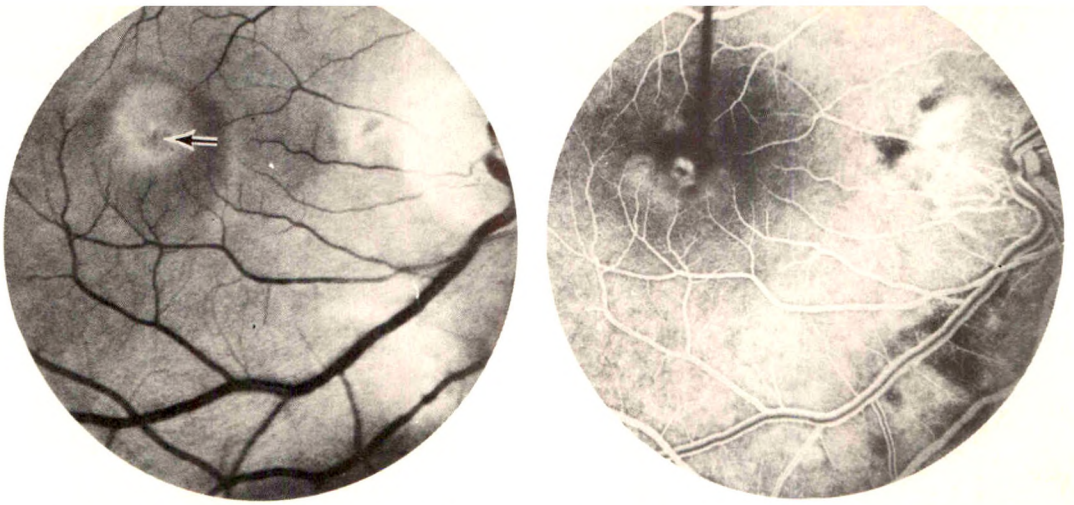

Fig. 4 (Vine and Schatz). Case 15. Left, Right macula, 20 months later. Small hemorrhage (arrow) present within yellow lesion. Right, Right macula, fluorescein angiogram. Area of early hyperfluorescence within yellow lesion indicating subretinal neovascularization.

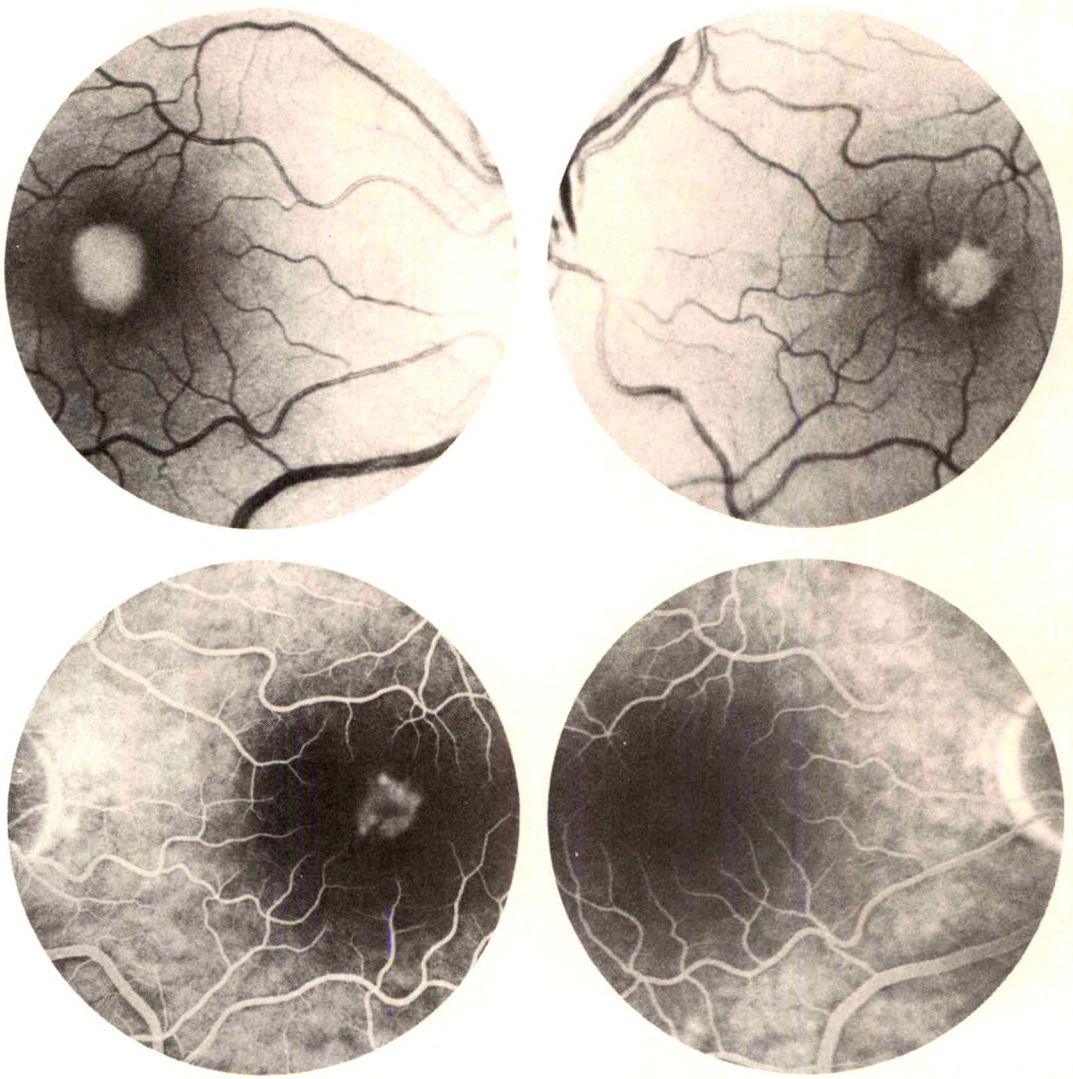

Fig. 5 (Vine and Schatz). Case 18. Top left, Right macula, yellow subretinal foveal lesion. Top right, Left macula, similar yellow subretinal foveal lesion. Bottom left, Left macula, fluorescein angiogram. A ring of hyperfluorescence surrounds a central area of hypofluorescence. Bottom right, Right macula, fluorescein angiogram. No hyperfluorescence in macula.

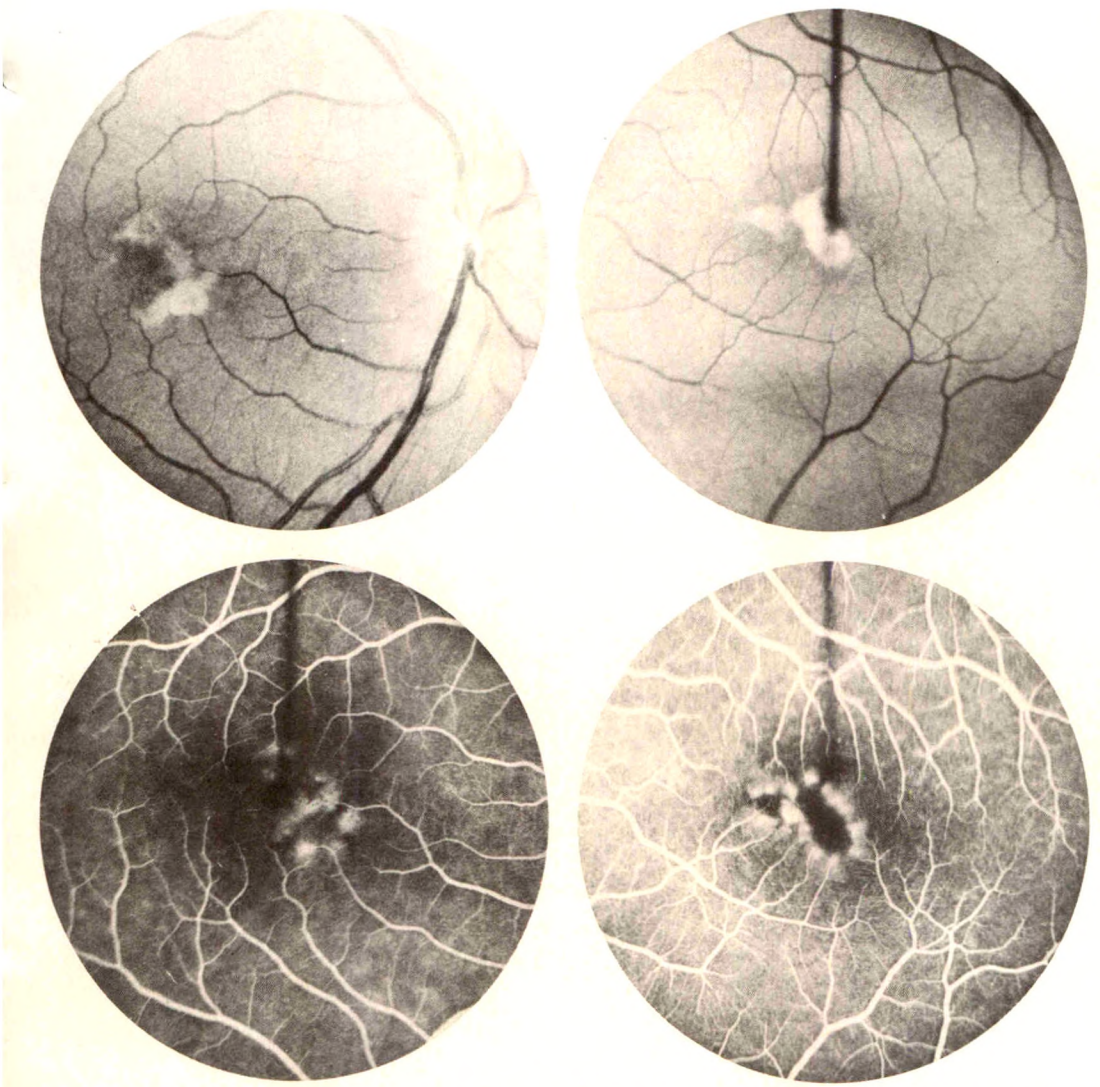

Fig. 6 (Vine and Schatz). Case 28. Top left, Right macula. Top right, Left macula. Two discrete foci of yellow subretinal material in each macula. Bottom left, Right macula, fluorescein angiogram. Bottom right, Left macula, fluorescein angiogram. Two incomplete rings of hyperfluorescence are present in each macula.

affected eyes has remained stable or deteriorated minimally.

Six patients have been followed up for at least 20 months. During this period, visual acuity of three of the patients has not changed and, in one patient, visual acuity has been minimally altered from 6/9 (20/30) to 6/12 (20/40) in the better eye. Case 15 was followed up for 25 months; visual acuity in the patient's better eye changed from 6/9 (20/30) to 6/15 (20/50). A subretinal neovascular net was also present in this macula. The remaining patient (Case 12) has had a marked decrease in visual acuity from R.E.: 6/9 (20/30) and L.E.: 6/12 (20/40) initially to R.E.: 6/60 (20/200) and L.E.: 6/30 (20/100) during a four-year period. In this patient, the bilateral yellow macular lesions have been slowly absorbed

TABLE 1

DATA OF 33 PATIENTS WITH UNIQUE ADULT-ONSET FOVEOMACULAR DYSTROPHY*

Case No., Age (yrs), Race, Sex		Visual Acuity	Subretinal Yellow Lesion	EOG†	Comment
1, 61, W,F	R.E.:	6/60 (20/200)	+	1.0	Vision stable for 1½ yrs
	L.E.:	6/12 (20/40)	+	1.0	
2, 56, W,M	R.E.:	6/9 (20/30)	+	ND	Vision stable for 1 yr
	L.E.:	6/9 (20/30)	Normal	ND	
3, 64, W,M	R.E.:	6/9 (20/30)	+	ND	Vision stable for 1 yr
	L.E.:	6/12 (20/40)	Normal	ND	
4, 69, W,F	R.E.:	6/9 (20/30)	+	ND	
	L.E.:	6/9 (20/30)	+	ND	
5, 68, W,F	R.E.:	6/9 (20/30)	+	1.1	
	L.E.:	6/12 (20/40)	+	1.2	
6, 76, W,M	R.E.:	6/9 (20/30)	+	ND	
	L.E.:	6/9 (20/30)	+	ND	
7, 64, W,F	R.E.:	6/9 (20/30)	+	ND	Vision stable for 1 yr
	L.E.:	6/9 (20/30)	+	ND	
8, 42, W,F	R.E.:	6/12 (20/40)	+	1.5	Sister has similar foveal lesion
	L.E.:	6/12 (20/40)	+	1.5	
9, 77, W,M	R.E.:	6/21 (20/70)	+	1.1	Argon laser therapy for subretinal neovascularization of the right eye
	L.E.:	6/60 (20/200)	+	1.2	
10, 69, W,M	R.E.:	6/60 (20/200)	+	ND	
	L.E.:	6/21 (20/70)	+	ND	
11, 50, W,M	R.E.:	6/9 (20/30)	+	1.8	Vision unchanged in 3 yrs
	L.E.:	6/4.5 (20/15)	+	1.7	
12, 66, W,F	R.E.:	6/9 (20/30)	+	1.8	Marked drusen bilaterally; both lesions replaced by atrophic changes during 4 yrs
	L.E.:	6/12 (20/40)	+	2.3	
13, 48, W,F	R.E.:	6/12 (20/40)	+	1.6	Bilateral midperipheral pigmentary changes
	L.E.:	6/12 (20/40)	+	1.4	
14, 80, W,M	R.E.:	6/30 (20/100)	+	1.7	
	L.E.:	6/60 (20/200)	+	1.7	
15, 57, W,M	R.E.:	6/9 (20/30)	+	1.8	Developed bilateral submacular neovascularization
	L.E.:	6/60 (20/200)	+	2.0	
16, 45, W,F	R.E.:	6/21 (20/70)	+	2.1	
	L.E.:	6/9 (20/30)	+	2.0	
17, 75, W,F	R.E.:	6/30 (20/100)	+	ND	Mother of Patient 18

*EOG designates electro-oculogram; ND, not done; and +, present.
†The lower limit of normal is 1.65 with our equipment.

and replaced with complete atrophy of the retinal pigment epithelium and choriocapillaris.

Of the 20 reported EOGs, 13 were normal (the lower limit of normal is 1.65 with our equipment), three were subnormal (1.40 to 1.60), and four were abnormal (1.00 to 1.20).

DISCUSSION

Recently, a variety of macular lesions have been described as "vitelliform" that do not appear to be classic examples of Best's disease. In 1974, Gass[1] described nine adult patients who had "a peculiar foveomacular dystrophy" that consisted of a ⅓ disk diameter, yellow, subretinal lesion with a central pigmented spot and associated normal or slightly subnormal EOG. In his book on macular diseases, in 1977, Gass[2] referred to this entity as "foveomacular vitelliform dystrophy: adult type." The patients described by Gass had similar visual acuities, macular

TABLE 1

DATA OF 33 PATIENTS WITH UNIQUE ADULT-ONSET FOVEOMACULAR DYSTROPHY* *(Continued)*

Case No., Age (yrs), Race, Sex		Visual Acuity	Subretinal Yellow Lesion	EOG†	Comment
	L.E.:	6/21 (20/70)	+	ND	
18, 50, W,F	R.E.:	6/21 (20/70)	+	1.9	Daughter of Patient 17
	L.E.:	6/6 (20/20)	+	1.9	
19, 77, W,F	R.E.:	6/21 (20/70)	+	1.7	
	L.E.:	6/60 (20/200)	+	1.7	
20, 78, W,M	R.E.:	1.2/60 (4/200)	Atrophic	1.7	Right eye showed foveal atrophy
	L.E.:	6/15 (20/50)	+	1.8	of pigment epithelium
21, 61, W,M	R.E.:	6/21 (20/70)	+	1	
	L.E.:	6/30 (20/100)	+	1	
22, 57, W,M	R.E.:	6/21 (20/70)	Atrophic	ND	
	L.E.:	6/9 (20/30)	+	ND	
23, 66, W,F	R.E.:	6/15 (20/50)	+	ND	
	L.E.:	6/12 (20/40)	+	ND	
24, 77, W,F	R.E.:	6/21(20/70)	+	ND	
	L.E.:	6/30 (20/100)	Atrophic	ND	
25, 54, W,F	R.E.:	6/9 (20/30)	+	ND	Perifoveal satellite lesion
	L.E.:	6/9 (20/30)	Normal	ND	present in the right macula
26, 52, W,F	R.E.:	6/21 (20/70)	+	1.6	
	L.E.:	6/9 (20/30)	+	1.6	
27, 80, W,F	R.E.:	6/21 (20/70)	+	ND	
	L.E.:	6/9 (20/30)	Normal	ND	
28, 37, W,F	R.E.:	6/6 (20/20)	+	1.65	Two adjacent parafoveal lesions
	L.E.:	6/9 (20/30)	+	1.70	present in each macula
29, 75, W,M	R.E.:	6/12 (20/40)	Normal	ND	History of ischemic optic
	L.E.:	6/60 (20/200)	+	ND	neuropathy of the left eye
30, 42, B,M	R.E.:	6/9 (20/30)	+	1.6	Sister has similar macular lesions
	L.E.:	6/60 (20/200)	+	1.6	
31, 64, W,M	R.E.:	6/9 (20/30)	+	2.4	No change in vision during 1 yr
	L.E.:	6/15 (20/50)	+	2.1	
32, 64, W,F	R.E.:	6/15 (20/50)	+	1.4	
	L.E.:	6/21 (20/70)	+	1.5	
33, 50, W,F	R.E.:	6/21 (20/70)	+	1.8	
	L.E.:	6/6 (20/20)	+	1.9	

findings, and identical fluorescein angiographic patterns as found in our patients.

Three adult patients with "pseudovitelliform macular degeneration" have also been described.[3] Such patients showed a ¾ to ⅓ disk diameter yellow lesion at the macula associated with a normal EOG. Fluorescein angiography showed leakage from perifoveal retinal capillaries. This disease entity appears to be separate from that found in our series because perifoveal leakage was not found in any of our patients or in those described by Gass.[1]

Kingham and Lochen[4] described lesions they termed "vitelliform macular degeneration." The six patients in their report showed a mild decrease in visual acuity associated with a submacular yellow accumulation. Fluorescein angiography showed no evidence of perifoveal leakage but did show slight hyperfluorescence surrounding the vitelliform lesion that was thought to be caused by rarefied retinal pigment epithelium. All EOGs

TABLE 2

VISUAL ACUITY OF AFFECTED EYES

Range	No.	Percent
6/6 (20/20)-6/15 (20/50)	35	60.4
6/18 (20/60)-6/30 (20/100)	15	25.7
6/60 (20/200)-3/60 (10/200)	8	13.9
Total	58	100

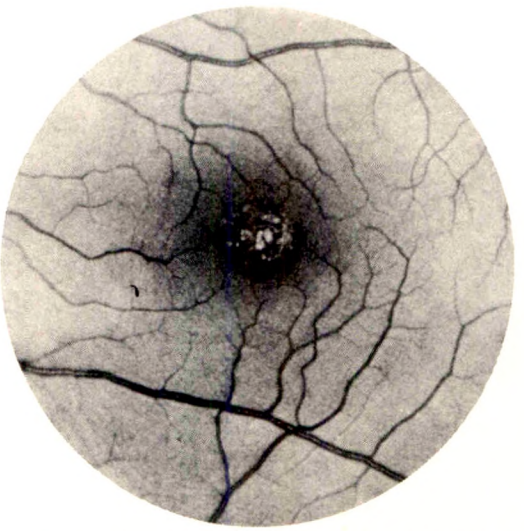

Fig. 7 (Vine and Schatz). Left macula. Confluent macular drusen.

were normal. These patients were similar to our patient sample except that Kingham and Lochen[4] could find no evidence of familial involvement.

Singerman, Berkow, and Patz[5] described ten family members with a "dominant, slowly progressive, macular dystrophy." Although there was a wide spectrum of macular changes in the affected family members, some patients showed subretinal foveal yellow-gray material with central, darker, gray material. The younger family members showed only a mild decrease in vision but their older relatives tended to have poor vision that was associated with atrophy of the pigment epithelium. In some cases, fluorescein angiography showed an ovoid area of hyperfluorescence surrounding the foveal lesions. Three of their 18 cases had EOGs that were reported as normal except for one eye that showed a reduced light/dark ratio. The results of Singerman, Berkow, and Patz[5] are pertinent to our study in that they present evidence for a dominant dystrophy, and some of their patients appear similar to the patients in our present series.

Confluent macular drusen must be considered in the differential diagnoses of yellow subretinal lesions. Numerous drusen involving only the macula (Fig. 7) can mimic a similar disease state. However, the macular changes we report can be distinguished from drusen by the homogenous nature of the subretinal yellow material and the presence of central or peripheral hyperpigmentation, or both. Macular drusen also have different angiographic features with early discrete hyperfluorescence that fades in the later angiogram.

We have seen one patient, a 53-year-old white man, with Best's disease who had macular changes similar to those seen in patients in our current series. He had no visual complaints, but showed a yellow, parafoveal, subretinal 400-μ lesion in the left macula; whereas five similar, smaller, separate, yellow accumulations were distributed in a parafoveal arrangement in his right macula. His spouse showed normal maculae. The couple's 29-year-old son showed the classic lesions of Best's disease. Also, this 29-year-old patient had a 3-year-old son who had a "scrambled egg" lesion in each macula.

Although Best's disease varies considerably in manifestation,[6] the macular lesions of our patients can be distinguished from the lesions seen in the vitelliform stage of Best's disease. In contrast to our patients, the vitelliform

stage of Best's disease usually occurs between the ages of 3 and 15, but it can also be observed in middle-aged or older individuals.[7] The yellow subretinal macular lesions of our patients are considerably smaller than the classic egg yolk lesions that occur in Best's disease.[7] None of our patients have developed layering of their subretinal yellow material (called pseudohypopyon) that is seen in Best's disease. The characteristic fluorescein angiogram pattern of our patients has not been reported in Best's disease.

In Best's disease, the EOG is classically markedly reduced.[7] In contrast, most of our patients had normal or slightly subnormal EOGs. Four of our patients, however, did have severely reduced EOGs (1.0 to 1.2). In Gass' series of nine patients with similar macular findings, one patient also had an abnormal EOG of 1.0 bilaterally. Although the EOG is a useful test, a definitive diagnosis of Best's disease or adult-onset foveomacular pigment epithelial dystrophy cannot be made on the basis of an abnormal EOG ratio alone. Recent reports have shown normal EOG ratios in patients with typical vitelliform macular lesions.[8,9]

Similar yellow foveal lesions can be seen in patients who have idiopathic macular telangiectasis.[10] A 75-year-old man, who had bilateral macular telangiectasis, showed reduced visual acuity of R.E.: 6/15 (20/50) and L.E.: 6/21 (20/70). A yellow, intraretinal 400-μ lesion was present at each fovea (Fig. 8, top left). The patient showed no evidence of intraocular inflammation and was taking no known retinotoxic drugs. Angiography showed bilateral telangiectasis of the perifoveal retinal capillaries and bilateral cystoid macular edema in the later phases of the angiogram (Fig. 8, top right and bottom left). This patient has some similarities to those patients described by Fishman and associates,[3] but there was no actual telangiectasis of the leaking perifoveal retinal capillaries that were shown in Fishman's patients.

More extensive retinal disease was evident in Case 13. This patient had bilateral, yellow subretinal macular lesions in addition to the bone spicule pigment clumping in the midperiphery found in retinitis pigmentosa. Although the scotopic responses of the electroretinogram were reduced in amplitude, there was no prolongation of the implicit time that is typically seen in retinitis pigmentosa. There is little likelihood that foveomacular pigment epithelial dystrophy is associated with retinitis pigmentosa because a recent review of macular lesions associated with a retinitis pigmentosa[11] failed to indicate any patients who fit our maculopathy description.

Two of our patients did develop subretinal neovascularization. Subretinal neovascularization occurs in many macular diseases including dominant drusen, myopic degeneration, angioid streaks, presumed ocular histoplasmosis syndrome, and the like.[10] None of the patients had subretinal neovascularization in Gass' series,[1] or in the reports by Fishman and associates,[3] and Kingham and Lochen.[4] On initial examination, our patient in Case 9 showed a visual acuity of R.E.: 6/21 (20/70) and L.E.: 6/60 (20/200). A yellow, subretinal parafoveal lesion was present in the right macula and a larger, yellow, subretinal, foveal lesion was present in the left macula. Fluorescein angiography showed parafoveal subretinal neovascularization in the right eye that was successfully treated with argon laser photocoagulation. Seventeen months after treatment, the patient's visual acuity remained 6/21 (20/70) in the right eye. As previously described, the patient in Case 15 had evidence of bilateral submacular neovascularization associated with foveomacular pigment epithelial dystrophy. The development of subretinal neovascularization in adult-onset

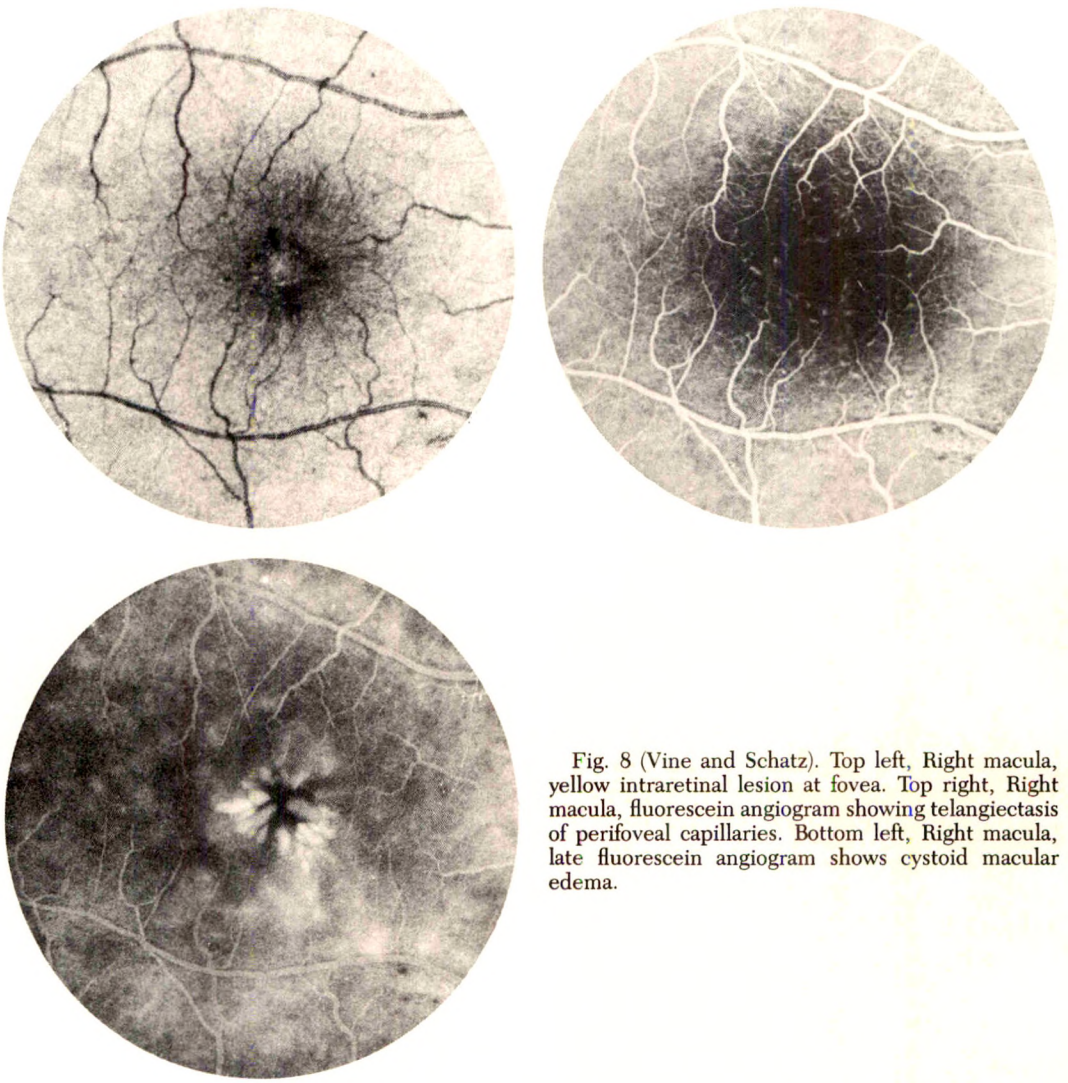

Fig. 8 (Vine and Schatz). Top left, Right macula, yellow intraretinal lesion at fovea. Top right, Right macula, fluorescein angiogram showing telangiectasis of perifoveal capillaries. Bottom left, Right macula, late fluorescein angiogram shows cystoid macular edema.

foveomacular pigment epithelial dystrophy should be considered unusual as it was seen in only three of 58 affected eyes.

As we do not have histopathologic material, we can only speculate as to the probable ocular abnormalities of our patients. By slit-lamp examination and stereofluorescein angiography, the foveal yellow material and pigment clumps were located deep to the sensory retina at the level of the retinal pigment epithelium. During fluorescein angiography, the pigment clumps appeared as hypofluorescent areas that were generally surrounded by a circle of hyperfluorescence. These clinical findings were also seen in Gass' series of patients where pathologic examination of one patient's eyes showed pigment-laden cells and extracellular pigment clumped in the fovea that was surrounded by a zone of atrophic pigment epithelium beneath which there was an accumulation of granular eosinophilic material. We believe that similar histopathologic changes

are probably present in our present series of patients.

Familial studies of some of our patients suggested an autosomal dominant transmission. The 44-year-old sister of Patient 8 has similar macular findings. Patient 18, the daughter of Patient 17, showed macular lesions similar to her mother's. An extensive examination of other family members, however, was inconclusive regarding any inheritance pattern. Patient 30 and her 46-year-old sister had similar macular lesions. Gass' series[1] was also suggestive of an autosomal dominant transmission. In contrast, Kingham and Lochen[4] emphasized the degenerative nature of the vitelliform lesions they described and could find no familial involvement. We believe that the bilateral, symmetrical lesions, and evidence of an autosomal dominant transmission suggests that this is a familial foveal macular dystrophy. We have chosen the name "adult-onset foveomacular pigment epithelial dystrophy" as a descriptive term because the macular lesions appear only in adult patients and are clinically located at the level of the retinal pigment epithelium.

Summary

Thirty-three patients had adult-onset foveomacular dystrophy. The macular lesions typically resulted in a mild to moderate decrease in vision and appeared as small, yellow, bilateral, slightly elevated, pigment epithelial lesions with areas of hyperpigmentation. The characteristic finding on fluorescein angiography was a ring of hyperfluorescence surrounding an area of hypofluorescence. The electro-oculograms were either normal or slightly subnormal in most cases. This dystrophy appears to have an autosomal dominant transmission.

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VISUAL LOSS IN RETINITIS PIGMENTOSA

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Retinitis pigmentosa typically begins in the equatorial retina, and progresses both anteriorly and posteriorly until only a tiny central island of visual field remains. Both cones and rods are involved, but damage to the rod system is most prominent and the effects on central vision are variable. Some patients maintain good visual acuity throughout their lives, despite unrecordable electroretinograms and 2- to 3-degree central fields. However, others lose central vision at a young age and are much more severely disabled.

The manner in which visual acuity changes with age is important to patients with this disease, but the course of visual loss in retinitis pigmentosa has never been established. Surveys have shown that roughly 50% of patients with retinitis pigmentosa have visual acuity of 6/15 (20/50) or worse and that the proportion of patients with poor visual acuity increases with age.[1–3] However, these data are based upon the visual acuity at a single examination. Thus, they are influenced by the selection of patients seeking care and do not show whether the loss of vision is gradual, step-wise, or abrupt.

I investigated the visual history of 91 consecutive patients who have typical retinitis pigmentosa, to determine when and how fast central vision was affected. The results imply that visual loss is rapid and unpredictable.

SUBJECTS AND METHODS

The population studied comprised all patients I saw in consultation and made a diagnosis of conventional retinitis pigmentosa, from July 1973 through September 1978. The diagnosis of retinitis pigmentosa was confirmed by electrophysiologic recordings for most of these patients, but in some was made clinically. Patients with mild variants of retinitis pigmentosa such as sectorial disease or delimited disease[4] were excluded, but their exclusion has little influence upon these results because almost all of these patients maintain good visual acuity. Also excluded were variants of retinitis pigmentosa such as centroperipheral disease, Laurence-Moon-Biedl syndrome or cone dystrophy, and patients in whom an acquired degeneration was suspected. A total of 91 patients with 179 nonamblyopic eyes fit the criteria. The probable mode of inheritance, determined by family history, was sporadic or recessive for 140 eyes (71 patients: 46 male, 25 female), dominant for 27 eyes (14 patients: ten male, four female), and X-chromosome-linked for 12 eyes (six patients: all male). Because of the small number of eyes with dominant and X-chromosome-linked retinitis pigmentosa, most of the results are presented only for recessive disease.

The visual history was investigated for every patient whose corrected visual acuity, at the time of latest examination by me, was 6/12 (20/40) or worse in either eye. Hospital charts, physician's records, and optometry records were examined or reviewed by telephone, until a best

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corrected visual acuity of 6/9 (20/30) or better in both eyes could be shown or until no further information could be located. No attempt was made to show any findings other than visual acuity, because the quality of past observations could not be verified personally.

Results

For each eye with recessive retinitis pigmentosa, the latest visual acuity was plotted against age (Fig. 1). The scatter of points indicates that the relationship of visual acuity to age cannot be a simple monotonic function. Instead of clustering along a diagonal between good vision in youth and poor vision in old age, the points are concentrated in overlapping ranges of good visual acuity (6/12 [20/40] or better) or poor visual acuity (6/60 [20/200] or worse). By my own examination, all of these patients, regardless of visual acuity, showed foveal abnormalities that usually consisted of an absence of foveal reflexes and irregularity of the vitreoretinal interface. Except for a few patients with severe visual loss, who showed marked pigmentary atrophy under the fovea, there was no obvious correlation between visual acuity and foveal appearance. Only two patients in this series (both with recessive disease) had cataracts of possible visual significance, but both also showed prominent foveal abnormality.

To determine the age and speed at which vision was lost, the previous visual history was investigated for the 116 eyes that had a corrected visual acuity of 6/12 (20/40) or worse. A total of 31 eyes could not be traced beyond 6/60 (20/200) visual

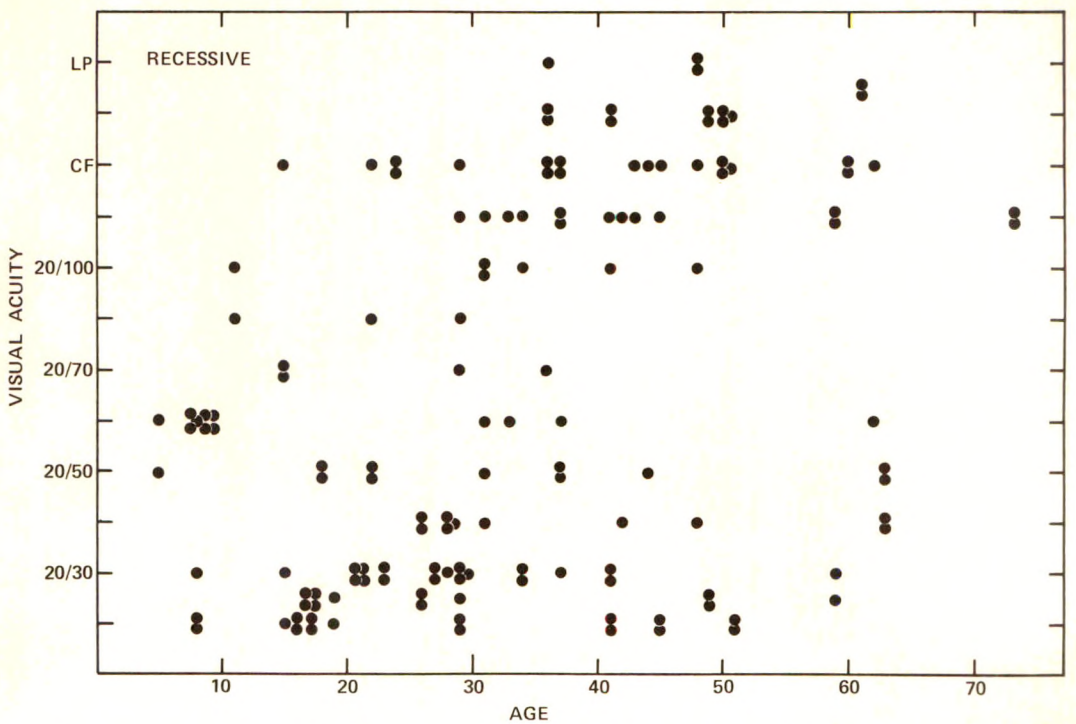

Fig. 1 (Marmor). Visual acuity at latest examinarion vs age, for cases with probable recessive inheritance. Each point represents one eye. The divisions of visual acuity in this and the following illustration are as follows: 6/6 (20/20), 6/9 (20/30), 6/12 (20/40), 6/15 (20/50), 6/18 (20/60), 6/21 (20/70), 6/24 (20/80), 6/30 (20/100), 6/60 (20/200), counting fingers, hand movements, and light perception.

acuity because old records or the patient could not be located. Figure 2 is a graphic representation of the visual history of the 59 eyes with recessive disease for which the visual acuity was traceable over a minimum change of three lines, or five years of follow-up, or to an earlier measurement of 6/12 (20/40) or better. There is a striking homogeneity in the slopes of the lines that represent visual change. The prevailing slope is steep, and indicates that the median time for a change in visual acuity from 6/12 (20/40) to 6/60 (20/200) was approximately six years, and the change occurred in less than ten years for all but a few patients. Additionally, visual acuity was lost with a relatively even distribution over ages five to 60 years. Eyes with dominant and X-chromosome-linked disease lost visual acuity with a similar time course, but there were too few cases to compare in terms of age. Statistical analysis of these data was considered, but our consultant believed that graphic presentation of Figure 2 was more direct and accurate because eyes differed greatly in age at first or last examination, duration of follow-up, and frequency of follow-up.

Visual acuities were compared between the eyes of patients with recessive disease, to determine how often the loss of visual acuity was unilateral or bilateral. Only 21% of the patients showed a difference of more than two lines of visual acuity between the eyes, but many of these individuals were young (with good visual acuity), whereas others had been legally blind in both eyes for years. Among cases for which a progressive loss of visual acuity could be historically documented, approximately 40% showed significant asymmetry of vision for five or more years.

The prevalence of visual loss in ocular disease has usually been calculated from data gathered at a single examination, a method that depends greatly upon the

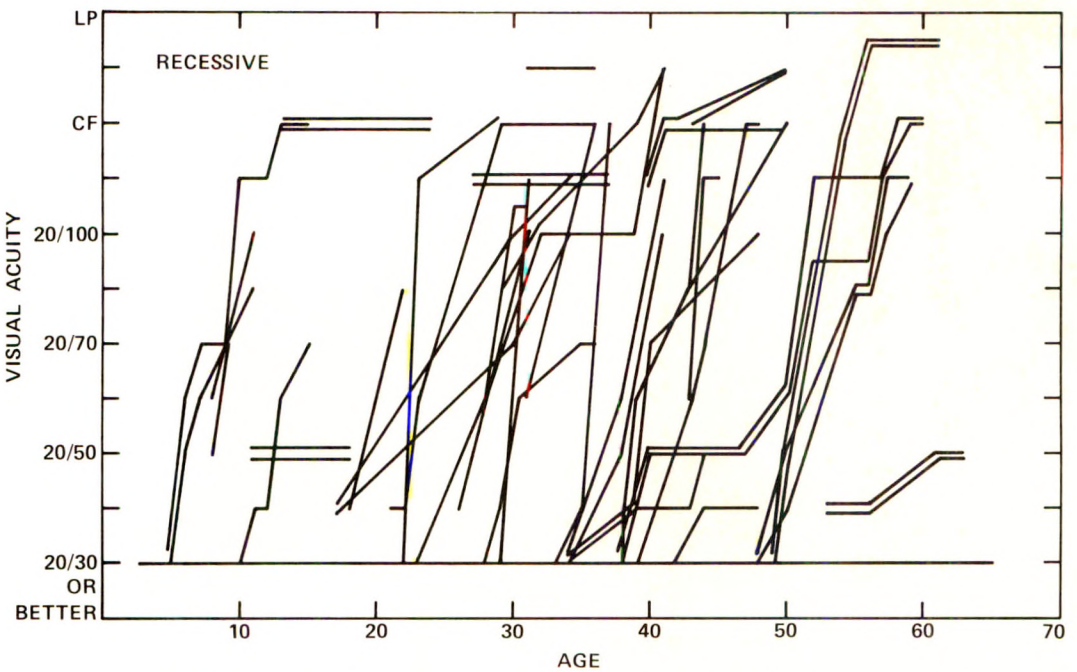

Fig. 2 (Marmor). Visual history of eyes with recessive retinitis pigmentosa. Each line connects all recorded visual acuities for one eye; only eyes that could be traced over five years or a three-line change in visual acuity are shown. Visual acuities of 6/9 (20/30) or better are not discriminated in this figure.

size and age distribution of the population being studied. These problems can be minimized, and more accurate data obtained from a small population, if the visual acuity of each eye at different ages throughout life is incorporated into the statistics. Figures 3 and 4 show the result of such an analysis from the present data for recessive and dominant retinitis pigmentosa. The current visual acuity of each eye was tabulated within the decade of the patient's most recent examination, but the worst visual acuity within each preceding decade (obtained from the visual history) was also tabulated. Thus, the youngest decade cumulated data from the entire sample. This method was straight-forward for individuals with a complete visual history; once an eye was noted to have good visual acuity (defined as 6/12 [20/40] or better for these plots) it was presumed to have good visual acuity in younger age groups. However, a problem developed for eyes that could not be fully traced. Because the dates of visual loss were unknown for these eyes, their visual acuities were indeterminate in decades that preceded their earliest examination. For presentation in histograms, these indeterminate visual acuities have been divided into two groups, depending on whether the earliest known visual acuity was midrange (6/15 [20/50] to 6/30 [20/100]) or poor (6/60 [20/200] or worse).

The resulting frequency plot for the 140 eyes with recessive disease (Fig. 3) shows clearly that the percentage with good visual acuity decreases steadily over

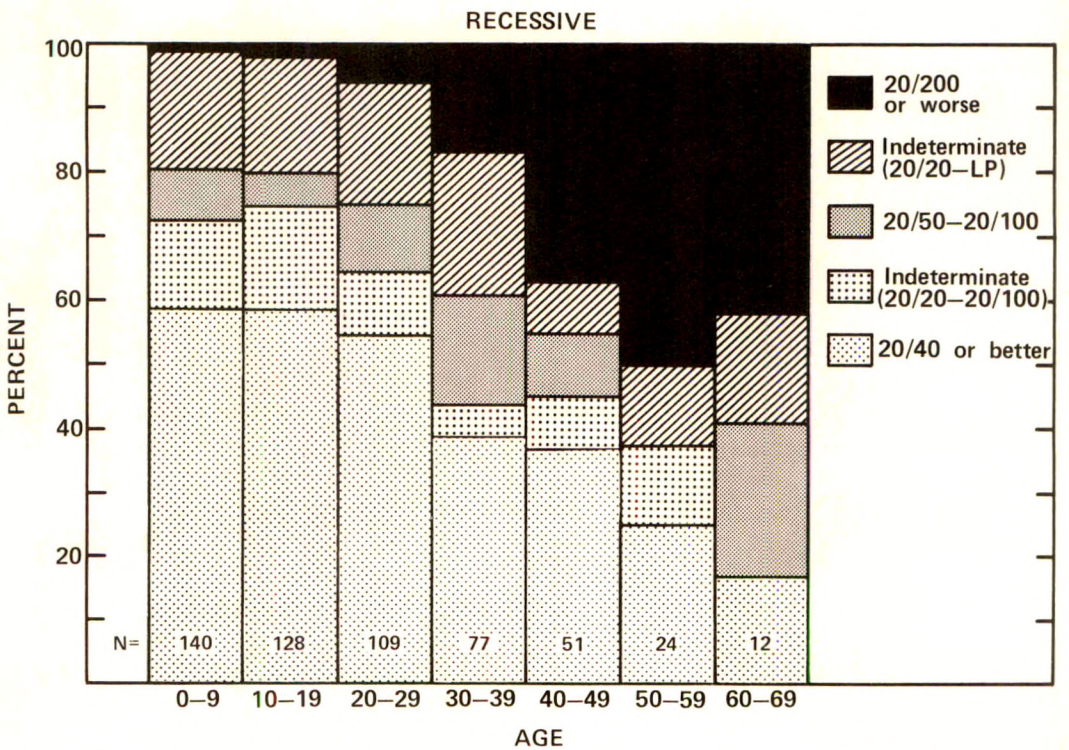

Fig. 3 (Marmor). Prevalence of different levels of visual acuity, at different ages, for eyes with recessive retinitis pigmentosa. Visual acuity is divided into three categories: good (6/12 [20/40] or better); midrange (6/15 [20/50] to 6/30 [20/100]); and poor (6/60 [20/200] or worse). The indeterminate ranges represent eyes whose earliest recorded visual acuity in an older age group was midrange or poor. The data were cumulated from older to younger age groups to incorporate all available historical information about each eye. The number of eyes in each category (N) is shown near the bottom of the histogram.

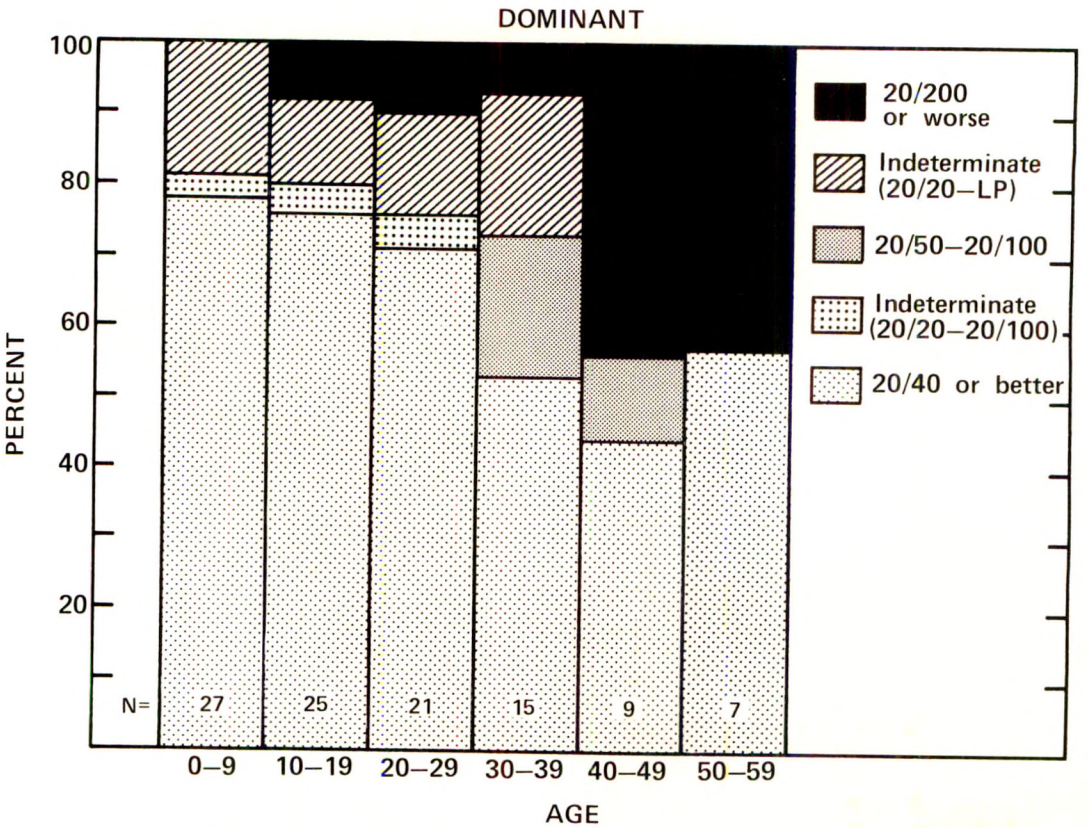

Fig. 4 (Marmor). Prevalence of different levels of visual acuity, at different ages, for eyes with dominant retinitis pigmentosa.

the years, whereas the percentage with poor visual acuity increases. The number of eyes with middle-range visual acuity remains relatively small (about 10%) throughout the plot, which is consistent with the impression from Figure 2 that visual acuity decreases rapidly at any age in retinitis pigmentosa and does not remain for any long period in the middle range. The 27 eyes with dominant disease (Fig. 4) showed a similar trend, and a somewhat larger percentage of eyes with good visual acuity at any given age.

Discussion

The data from recessive and sporadic cases of conventional retinitis pigmentosa show that the disease was unexpectedly rapid in its effects on visual acuity. Visual loss began at any age, and once visual acuity began to fail, it generally dropped to 6/60 (20/200) or below within a period of four to ten years (the median is near six). There appeared to be few cases in which midrange visual acuity (6/15 [20/50] to 6/30 [20/100]) was maintained for any period of time. Indeed, the data in Figure 2 may underestimate the speed of visual loss; the visual history lines pass through all of the available visual acuity measurements for each eye, but if no examinations were recorded over a long period of time (for example, ten years), then the line drawn between visual acuities at the beginning and end of that period may have a falsely shallow slope. In many patients the two eyes were affected simultaneously, but in 20 to 40% one eye was spared for five or more years.

Retinitis pigmentosa is not a homogeneous disease. Different modes of inheritance have been accounted for in this study, but there also may be unrecognized variants within each mode of inheritance. Some of the differences in visual history, among individuals, may reflect such variants.

The present data suggest that the progression of visual loss in dominant retinitis pigmentosa may be slightly slower, and occur at a slightly older age, than in recessive disease. However, because of the relatively small numbers of cases, and the variability among individuals, that conclusion could turn out to be unfounded. The classic view[3,5] has been that dominant disease is inherently milder, but one recent study[6] suggests that there is little distinction.

Prospective studies should ultimately be undertaken, but they are exceedingly difficult with retinitis pigmentosa because of the slow progression of the disease. Although this was a retrospective study in which information was obtained from old records and various sources, visual acuity is a relatively straight-forward measurement, and I did the last examination of all patients to insure that earlier measurements were consistent and that unrelated causes of poor visual acuity could be excluded.

The subjects of this report were all referred for diagnosis or counseling; thus, asymptomatic individuals were unlikely to be included, as were individuals with long-standing poor vision for whom consultation offered little benefit. This inherent bias of a referral population was minimized by tracing the visual history, but could still influence the prevalence data, especially at older ages.

Full visual histories were not obtainable for all eyes with poor vision in this study. The timing of visual loss was still uncertain for at least one eye of 20 of the patients, but there is no reason to expect that these individuals, who either could not be located or for whom no old records could be obtained, showed any different behavior than the individuals for whom a visual history was traced. The regions of indeterminate visual acuity in the prevalence histograms show the magnitude of the uncertainty that must be accepted until better data become available.

The cause of visual loss in retinitis pigmentosa has not been determined. Foveal pathologic findings such as absent reflexes, cystoid macular edema, or pigment epithelial atrophy were evident clinically in all of the present patients as well as in most patients with retinitis pigmentosa examined by others.[7,8] However, these changes may be present while central visual acuity is still good.[7,9] It is difficult to judge, therefore, whether a patient's loss of visual acuity results from primary damage to the photoreceptors or from a secondary degenerative phenomenon such as cystoid macular edema. Clearly clinical tests that are more subtle than Snellen visual acuity are needed to evaluate and follow up macular function in retinitis pigmentosa. Both color vision[10] and contrast sensitivity[11–13] may be abnormal in retinitis pigmentosa while visual acuity is still good. However, these tests are not sufficiently refined, as yet, to monitor the early stages of retinitis pigmentosa or to predict when visual loss is imminent.

The data presented in this report refer to conventional cases of retinitis pigmentosa and not those with anatomically or functionally limited disease such as sectorial retinitis pigmentosa or delimited retinitis pigmentosa.[4] Recognition of the latter cases is important because they may appear ophthalmoscopically similar to conventional retinitis pigmentosa, but they have mild symptoms and a much better visual prognosis. They are best distinguished by use of the electroretinogram that characteristically shows moderate amplitude and a normal cone b-wave implicit time.[4]

The results of this study have important implications for patient counseling. Others have shown that most patients with retinitis pigmentosa have significantly diminished visual acuity, and that the prevalence of good visual acuity decreases with age. However, the prevalence data in Figures 3 and 4 are the first, to the best of my knowledge, which have been calculated on the basis of previous as well as current information. These cumulative data show that more than 60% (and possibly as many as 90%) of patients with recessive and dominant retinitis pigmentosa under the age of 20 years have a visual acuity of 6/12 (20/40) or better; this percentage decreases to 25% (or up to 35%) by the 50s. Thus, few patients with retinitis pigmentosa will have 6/60 (20/200) or worse visual acuity before age 20 years, but by age 50 years at least 50% will be affected to that degree. Patients should be informed of these estimates to be aware not only of possible loss of vision, but of the hopeful aspects of the prognosis. For example, roughly 25% of patients with retinitis pigmentosa retain good reading vision throughout life, and the longer that good vision is retained, the better the chances of keeping it. Patients should also be aware that, in all hereditary groups of retinitis pigmentosa, the midranges of visual acuity seem to be unstable and carry a guarded prognosis. This latter observation may be of some use in research, because patients with visual acuity between 6/15 (20/50) and 6/30 (20/100) would be good subjects for the evaluation of new therapies, if secondary foveal changes can be ruled out as the cause of visual loss.

Summary

I investigated the visual histories of 91 consecutive patients with retinitis pigmentosa to determine when, and how fast, visual acuity was affected by the disease. The results from recessive cases showed that visual loss may occur at any age in retinitis pigmentosa, and typically progresses from 6/12 (20/40) to 6/60 (20/200) in about six years. At any given time, most of the patients had either good or poor visual acuity; intermediate levels of visual acuity appeared to be unstable. Before age 20 years, 60 to 90% of the patients had a visual acuity of 6/12 (20/40) or better, and few had a visual acuity of 6/60 (20/200) or worse. By age 50 years, 25% of the patients still retained good visual acuity, but more than 50% had visual acuity of 6/60 (20/200) or worse.

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COMPUTED TOMOGRAPHIC FEATURES IN OPTIC NEURITIS

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Monocular visual loss occurring in the presence of clear ocular media and a normal-appearing fundus usually indicates either a compressive or inflammatory lesion of the prechiasmal visual pathway. When the optic disk is swollen, an inflammatory papillitis or an orbital mass lesion again constitute the primary diagnostic considerations. In either setting, it is occasionally difficult to differentiate inflammatory from compressive lesions by the clinical history and examination. With the advent of computed tomography scan, mass lesions affecting the orbital portion of the optic nerve are readily identified. The configuration and enhancement qualities may even indicate a histologic diagnosis. There is, however, little information available regarding the characteristics of the computed tomography scan of either retrobulbar or intraocular optic neuritis. We describe the enlargement and enhancement of the optic nerve in two patients in whom the diagnosis was confirmed by the clinical course of the disease. We report herein the appearance of the computed tomography scan in one case of retrobulbar neuritis and one case of papillitis.

CASE REPORTS

Case 1—A healthy 14-year-old boy came to the Eye Clinic at the United States Air Force Hospital in Homestead complaining of sudden painless visual loss in the left eye on the previous day. Medical history revealed that three years previously he had undergone uneventful extraocular muscle surgery for congenital nystagmus that improved his visual acuity from 6/12 (20/40) to 6/7.5 (20/25) in each eye when measured in the primary position. On initial examination during this illness his visual acuity was R.E.: 6/7.5 (20/25) and L.E.: 6/120 (20/400). Within 72 hours, the visual acuity of the left eye decreased to no light perception; the right eye was unchanged. A left afferent pupillary defect was present. Both fundi appeared normal. The clinical impression was retrobulbar neuritis, but because of the progression to no light perception, a computed tomography scan was obtained to rule out the possibility of a compressive lesion.

The computed tomography scan showed that the entire intraorbital optic nerve of the left eye was diffusely enlarged with somewhat irregular margins (Fig. 1). The entire intraorbital nerve enhanced after the injection of contrast material (Fig. 2). The right optic nerve appeared normal. Three neuroradiologists interpreted these features as consistent with an optic nerve glioma.

No therapy was instituted. During the ensuing three months, vision in the left eye improved spontaneously. Visual acuity returned to 6/24 (20/80), although perimetry showed a dense central scotoma. The afferent pupillary defect remained, and pallor of the disk developed. A repeat computed tomography scan showed normal optic nerves without enhancement (Fig. 3). These reversible alterations in the left optic nerve confirmed the original clinical diagnosis of retrobulbar neuritis.

Case 2—A 21-year-old healthy woman had a two-week history of periorbital pain and slowly

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The opinions and assertions contained herein are the personal views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense or the United States Air Force.

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Fig. 1 (Howard, Osher, and Tomsak). Retrobulbar optic neuritis. Initial computed tomography scan without enhancement showing irregularly thickened left optic nerve.

Fig. 2 (Howard, Osher, and Tomsak). Retrobulbar optic neuritis. Initial computed tomography scan with enhancement of thickened left optic nerve.

progressive visual loss in the right eye. Three weeks before admission, a routine ophthalmologic examination showed visual acuity of 6/6 (20/20) in each eye.

Examination showed the best corrected visual acuity of counting fingers at 6 inches in the right eye and 6/6 (20/20) in the left eye. Pupillary testing showed a right afferent defect, reflecting the presence of a dense 30-degree central scotoma detected by formal perimetry. The right optic nerve appeared diffusely hyperemic and swollen, with a linear hemorrhage present on the superonasal disk margin. Results of the examination of the left eye were normal.

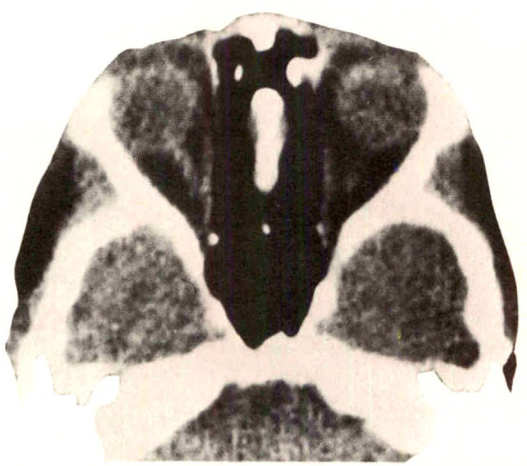

Fig. 3 (Howard, Osher, and Tomsak). Computed tomography scan showing normal optic nerves after resolution of left retrobulbar neuritis.

A computed tomography scan was obtained because of the history of pain and slowly progressive profound visual loss associated with unilateral disk edema. The intraorbital segment of the right optic nerve appeared irregularly thickened on both axial and coronal computed tomography scans, measuring 1.5 mm larger than the normal left optic nerve (Fig. 4). This asymmetry was present on plain and enhanced studies, and a diagnosis of glioma of the optic nerve was considered by the neuroradiologist. The patient was treated with 40 mg of periocular triamcinolone, and serial examinations over the subsequent five weeks showed a steady improvement in visual function. Visual acuity returned to 6/6 (20/20) without a detectable field defect, and the optic disk appeared normal. The clinical course confirmed the diagnosis of optic neuritis with optic nerve enlargement shown by computed tomography scan.

Discussion

To the best of our knowledge there are no previously published reports emphasizing an abnormal computed tomography scan in optic neuritis. A plethoric

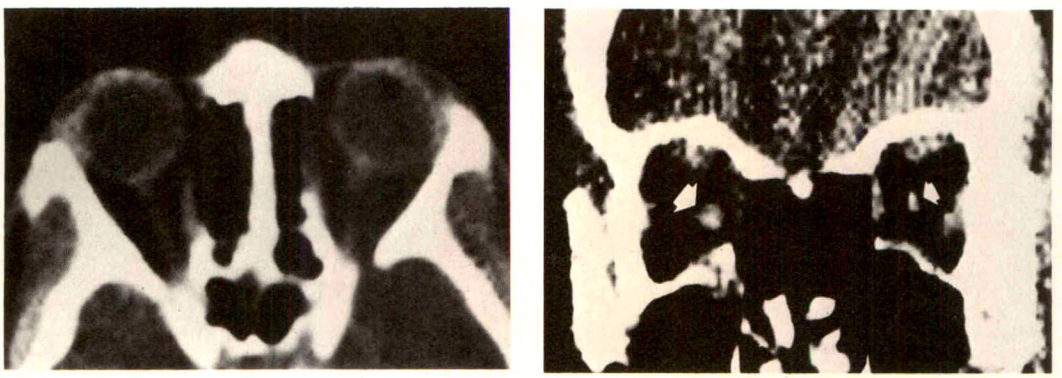

Fig. 4 (Howard, Osher, and Tomsak). Papillitis. Thickening and enhancement of right opitc nerve (large arrow) compared to normal left optic nerve (small arrow) present on axial computed tomography scan (left) and coronal computed tomography scan (right).

optic nerve has been described in a patient with Leber's optic neuropathy.[1] In a review of 603 orbital computed tomography scans, five patients with optic neuritis were noted to have large optic nerves.[2] Another study consisting of 67 computed tomography scans obtained for various ophthalmologic conditions showed unremarkable findings in five patients with optic neuritis.[3]

The demonstration of an enlarged optic nerve in this condition provides radiographic correlation of the anatomic changes that accompany the diminished visual function in optic neuritis. The optic nerve appears thickened and enhances with contrast material because inflamed neural tissue is associated with both vascular engorgement and increased vessel permeability as the blood-brain barrier is altered.[4] The thickened appearance reflects an edematous optic nerve, and secondary vascular changes account for contrast enhancement. In the case of retrobulbar neuritis, the entire intraorbital nerve was enlarged despite a normal-appearing optic disk.

Thickening and enhancement of the optic nerve must be considered a nonspecific finding. These features have been observed in papilledema, Grave's disease, inflammatory pseudotumor, central retinal vein occlusion, traumatic hematoma of the optic nerve sheath, and with tumors of the optic nerve, such as glioma and meningioma.[1,2,5]

As a general rule, the clinical appearance will readily differentiate optic neuritis from tumors involving the optic nerve. It is important that the clinician be aware of those inflammatory radiographic features that may be misinterpreted as neoplastic. In rare cases, when the clinical diagnosis is unclear, the recognition of reversible enlargement and enhancement of the optic nerve will provide evidence against the diagnosis of optic nerve tumor. Future computed tomographic studies will yield the frequency of radiographic changes in optic neuritis, and may even reveal a correlation between the initial changes seen on computed tomography scan and the eventual visual outcome.

Summary

A computed tomography scan obtained in two patients with monocular visual loss showed diffuse enlargement and enhancement of the intraorbital portion of the involved optic nerve. Al-

though these tomographic features were initially interpreted as an optic nerve glioma by the neuroradiologist, the ensuing clinical course established the diagnosis of optic neuritis.

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Fifty years ago this month in *The Journal:*

While the presence of increased intraocular pressure as the essential element of glaucoma was first recognized by Mackenzie about 1830, it is known that Himly and Beer were in the habit of palpating the globes of cases suspected of hardness. Bowman introduced the ratings of +1, +2, +3 for slight increase of tension, decided increase, and stony hardness; and −1, −2, −3 for corresponding reductions. There was much discussion whether the patient should look down when the tension was tested, because this increased the pressure of the lids upon the globe; at least so some said. Against this objection was advanced the interposition of the tarsal cartilage between globe and finger tip if the patient looked ahead or up. Coccius moistened his finger tips in tepid water and palpated the globe directly below the cornea while the patient looked upward. R. A. Fick (1888) suggested the use of a pig's eye connected with a manometer. The clinician could palpate the human eye and then the animal eye, and adjust the pressure of the latter until it seemed comparable with the human eye; whereupon the manometer reading could be made.

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DISAPPEARING OPTICOCILIARY SHUNT VESSELS AND PSEUDOTUMOR CEREBRI

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Many reports have been published in recent years on the presence of opticociliary venous shunts in association with optic nerve sheath meningiomas.[1–7] They have also been described in cases of optic nerve gliomas,[8] arachnoid cysts of the optic nerve,[9] optic nerve coloboma,[10] central retinal vein occlusion,[11] drusen of the optic disk,[12] chronic atrophic papilledema,[13] and in normal eyes.[10] We describe two patients with pseudotumor cerebri with apparent opticociliary venous shunts. One patient underwent bilateral optic nerve sheath fenestrations.

CASE REPORTS

Case 1—A 23-year-old woman came here in July 1977. She had a continuous throbbing headache of two-weeks' duration that was unresponsive to aspirin, decreased vision for one week, and diplopia for four days. Examination disclosed bilateral papilledema and a right sixth cranial nerve palsy believed to be secondary to increased intracranial pressure. Kinetic visual fields, performed on a Goldmann perimeter, revealed enlarged blind spots. Results of the remainder of the ophthalmologic examination were within normal limits, as were the results of physical and neurologic examinations. Skull x-ray films, computed tomography, and three-vessel arteriogram were all normal. Opening pressure on lumbar puncture was 410 mm H_20; examination of the cerebrospinal fluid was unremarkable. On repeat lumbar puncture three days later, opening pressure was 370 mm H_20. During her hospitalization, she was treated with a short course of dexamethasone (Decadron). She was discharged and followed up in the neurology clinic, where several outpatient lumbar punctures were performed, all revealing increased cerebrospinal fluid pressures.

She was lost to follow-up until February 1978 when she was seen in the emergency room complaining of chronic headaches. Lumbar puncture revealed an opening pressure of 400 mm H_20. Early visual field loss was documented in the chart.

She was again lost to follow-up until June 1978 when she returned to the eye clinic complaining of flashes and floaters in both eyes of two to three months' duration. She was able to read under a bright light but unable to drive. Visual acuity was R.E.: 6/6 (20/20) and L.E. 6/7.5 (20/25). Findings from the ophthalmic examination included a mild right sixth cranial nerve palsy and evidence of chronic papilledema with loss of nerve fiber bundles. Vessels resembling opticociliary shunts were seen on both disks (Fig. 1). Kinetic perimetry revealed nearly complete loss of the nasal field in both eyes as well as an inferior arcuate defect in the right eye and a superior arcuate defect in the left eye (Fig. 2).

She was admitted to the neurology service and was given 2 g of acetazolamide (Diamox), orally four times daily, glycerol, and fluid restriction. Daily lumbar punctures were performed with opening pressures ranging between 300 to 400 mm H_2O. Despite this regimen, she continued to lose visual fields in both eyes, and bilateral optic nerve sheath fenestrations were performed one week apart (Fig. 3). The papilledema diminished postoperatively, but her visual fields remained unchanged. Fluorescein angiography was performed on several occasions, in an attempt to show that the abnormal vessels on her disks were functioning as shunts. This could not be shown conclusively.

Since discharge, she has been followed up in the outpatient department. Although her cerebrospinal fluid pressures remain increased, the appearance of her disks, as well as her visual fields, have remained stable.

Case 2—In January 1979 a 39-year-old woman came here complaining of 14 years of progressively increasing headaches on the right side. They had increased in frequency from two to three per year to one or two per week, accompanied by nausea, vomiting, and photophobia. In 1970 she had been told of "pressure on her optic nerves." She was treated with prednisone.

In May 1978 she complained of persistent headache on the left side, and in August 1978 this was accompanied by blurred vision. At that time she was examined at another institution. Her visual acuity was noted to be R.E.: 6/6 (20/20) and L.E.: 6/7.5

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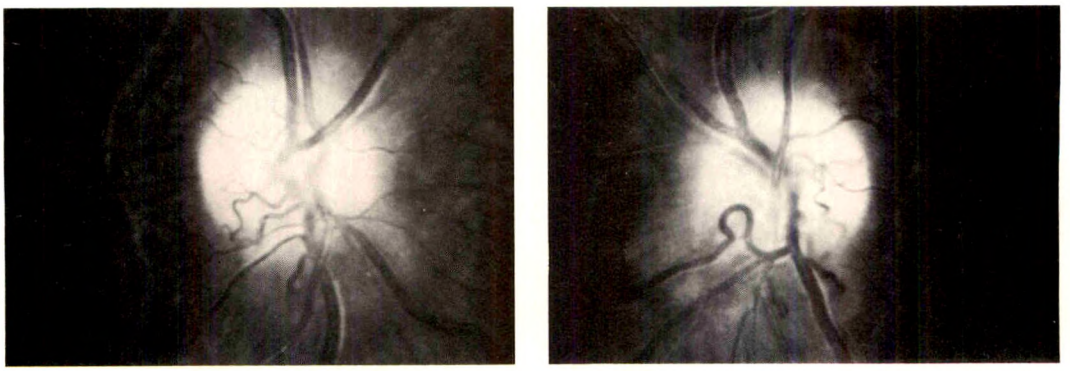

Fig. 1 (Perlmutter and associates). Vessels resembling opticociliary venous shunts are seen in both eyes. Evidence of chronic papilledema is present.

(20/25). She had bilateral papilledema, thought to be worse in her left eye. Her visual field in the left eye, tested on a tangent screen (3/1000 W), was constricted; the visual field in the right eye was also constricted with baring of the blind spot. Skull x-ray films, computed tomography, and bilateral carotid arteriography were all within normal limits. Lumbar puncture revealed an opening pressure of 250 mm H_2O. A diagnosis of pseudotumor cerebri was made, and she was given prednisone orally. Her headaches continued without relief, despite her use of acetazolamide (Diamox) taken orally and multiple lumbar punctures. Opening pressures ranged from 210 to 310 mm H_2O. Her visual fields reportedly improved.

Examination in our office in January 1979 showed visual acuity of 6/6 (20/20) in both eyes, an afferent pupillary defect in the left eye, and normal color vision in both eyes. On Amsler grid testing, only the central dot appeared blurred in the left eye, and normal in the right eye. Kinetic perimetry showed enlargement of the blind spot in the right eye and an inferior arcuate defect in the left eye (Fig. 4). Examination of her fundi revealed bilateral papilledema. Two abnormal vessels resembling opticociliary veins were seen in the left eye (Fig. 5). It was possible to show functioning venous shunt vessels by fluorescein angiography (Fig. 6). Results of her neurologic examination were otherwise within normal limits.

Skull x-ray films, optic canal polytomography, and technetium 99m scan were all normal. Computed tomography showed thickening and redundancy of both optic nerves. A-scan revealed enlargement of the left optic nerve as compared with the right optic nerve; no comment could be made as to whether this was secondary to enlargement of the nerve itself or dilation of the subarachnoid space. Lumbar puncture revealed an opening pressure of 270 mm H_2O within

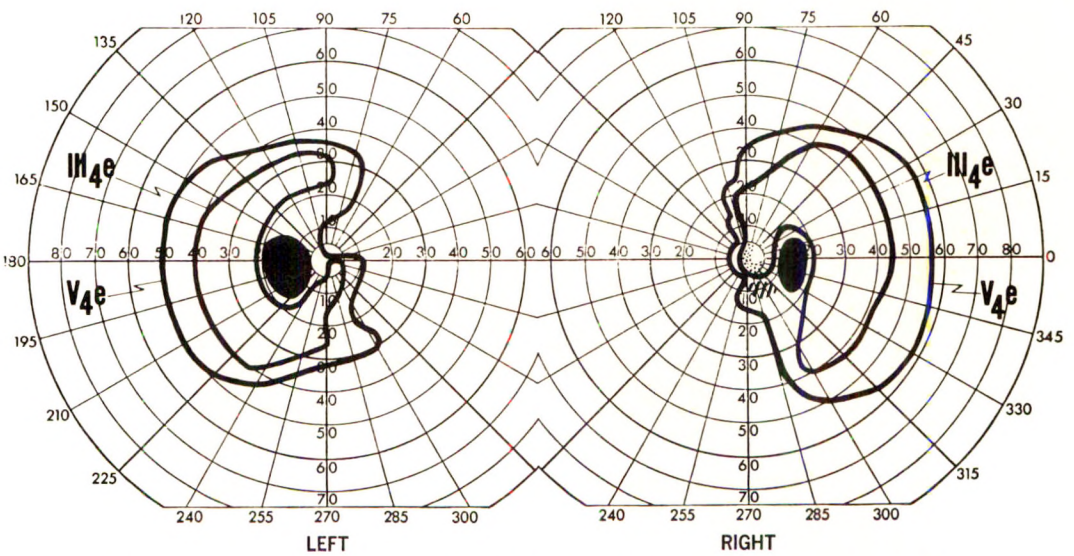

Fig. 2 (Perlmutter and associates). Case 1. Visual fields reveal severe bilateral loss of nasal field; an inferior arcuate defect is present in the visual field of the right eye and a superior arcuate defect in the visual field of the left eye.

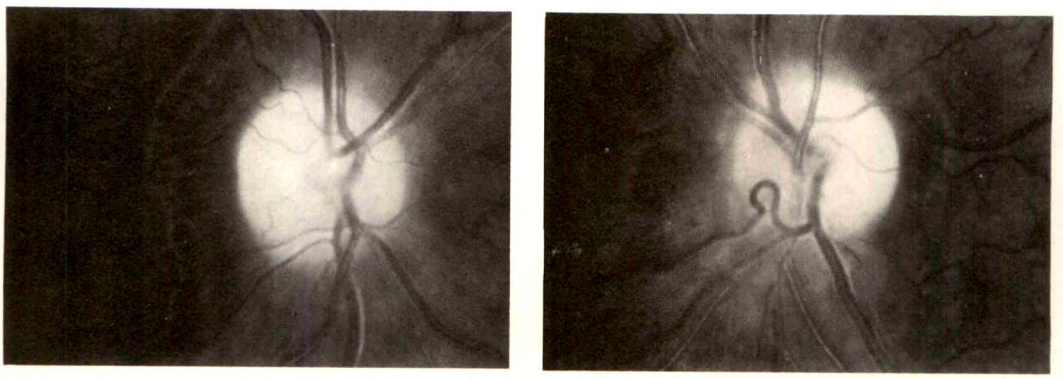

Fig. 3 (Perlmutter and associates). Disk photographs ten days postoperatively in the right eye (left) and three days postoperatively in the left eye (right) reveal marked narrowing of the apparent shunt vessels and partial resolution of papilledema.

normal limits and normal glucose and protein levels. A diagnosis of pseudotumor cerebri was made.

Discussion

Opticociliary venous shunts were described by Elschnig[10] in patients with papilledema and old glaucoma. Elschnig[14] and Salzmann[15] each described their presence in patients with optic nerve sheath meningiomas, microscopically tracing them to their junction with choroidal veins. Both believed these vessels represented dilated pre-existing capillaries bypassing compromised central venous outflow. Spencer[1] suggested that they might also be newly formed collaterals. Spencer,[1] Spencer and Hoyt,[2] and others[3–7] have emphasized the triad of pale disk edema, long-standing blindness, and opticociliary venous shunts. This is a specific clinical triad that indicates a meningioma of the anterior perioptic meninges.

Venous obstruction may be produced,

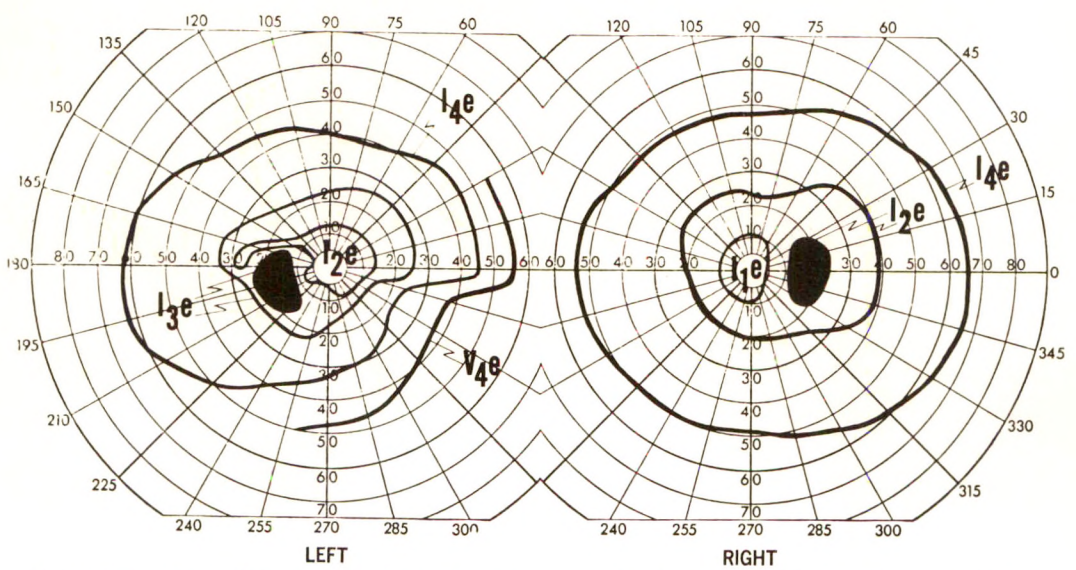

Fig. 4 (Perlmutter and associates). Case 2. Visual fields reveal enlargement of the blind spot in both eyes. An inferior arcuate defect is seen in the left eye.

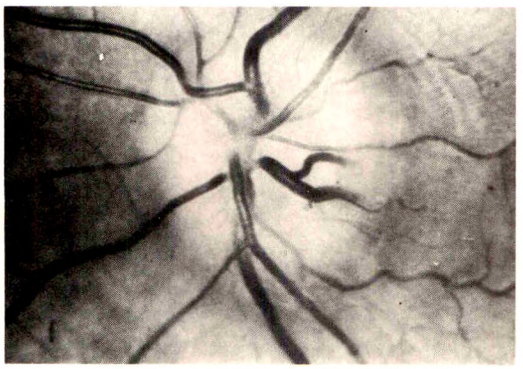

Fig. 5 (Perlmutter and associates). Case 2. Fundus photograph of the left eye shows evidence of papilledema, and two vessels resembling opticociliary venous shunts are seen inferotemporally.

however, by local compression of the central retinal vein within the optic nerve or subarachnoid space, either by a mass lesion or by chronically increased cerebrospinal fluid pressure transmitted along the subarachnoid space. Prelaminar venous channels then dilate, and blood following the path of least resistance flows into the choroidal system and exits from the globe via the vortex veins.

Lesions in and around the optic nerve, which result in elevation of the disk with blurring of its margins, produce disk edema. Papilledema specifically implies an increase of intracranial pressure. Changes in the disk secondary to papilledema are bilateral.

Patients with pseudotumor cerebri should be readily distinguishable from those with opticociliary venous shunts secondary to other uniocular abnormalities; for example, cysts of optic nerve, gliomas, drusen, central retinal vein occlusion, and the like. Further, computed tomography and polytomography should aid this differential diagnosis.

Galbraith and Sullivan,[16] and later Burde, Karp, and Miller,[17] described surgical decompression of the perioptic meninges of patients losing visual field secondary to chronic papilledema. In our Case 1, within three days of the first operation (right eye), there was marked regression both of disk edema and in the caliber of the apparent shunt vessels. No effect was seen on the contralateral eye, suggesting that the decompression acts locally and does not, at least initially, affect intracranial pressure. Similar postoperative changes were noted in the other eye.

Summary

In two patients opticociliary venous shunts occurred in association with pseudotumor cerebri. One patient underwent bilateral optic nerve sheath fenestra-

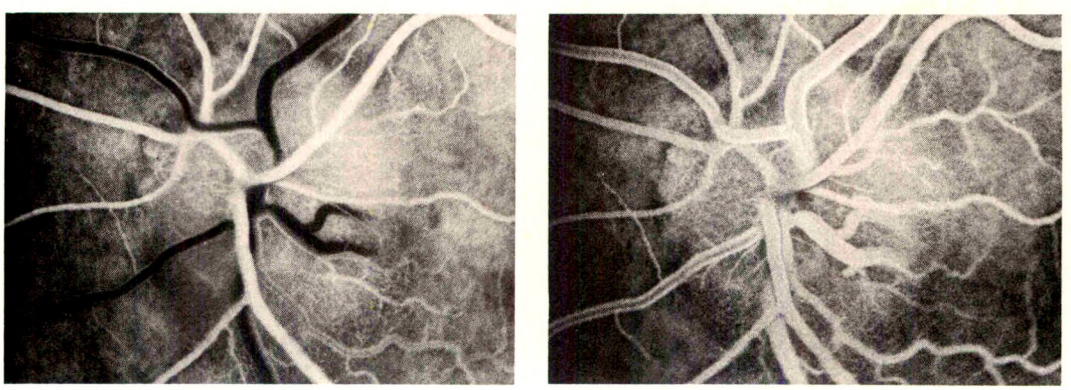

Fig. 6 (Perlmutter and associates). Early (left) and late (right) venous phase of fluorescein angiogram (fluorescein is white). Vessels are seen resembling opticociliary venous shunts. Veins on the disk ipsilateral to the shunt vessels appear full, whereas those contralateral to the shunt vessels remain in laminar flow (right).

tions, after which her papilledema resolved, and the opticociliary venous shunts were noted to be markedly decreased in caliber.

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TRANSIENT SUPRANUCLEAR DISTURBANCES OF GAZE IN HEALTHY NEONATES

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The eyes of a healthy, normal newborn infant are rarely aligned.[1] During the first few weeks of life they frequently shift between orthotropia and esotropia or exotropia. The exact frequency with which these deviations occur as well as anatomic and physiologic correlates of these transient neonatal heterotropias have yet to be defined. However, most infants apparently establish ocular alignment within several weeks of birth and exhibit no lasting ill effects from this temporary period of misalignment.

In addition to these simple horizontal misalignments a few reports have indicated that transient supranuclear disturbances of gaze may occur in the neonatal period.[2–4] The nature of these disturbances has been either a tonic downward deviation of the eyes[2,3] or opsoclonus.[4] The incidence and course of transient supranuclear disturbances of gaze in healthy neonates have not been detailed previously. We describe herein the incidence of tonic downward deviation of the eyes, opsoclonus, and skew deviation in 242 healthy neonates and the nature of each of these ocular motility disorders in these infants.

SUBJECTS AND METHODS

Two hundred forty-two consecutive healthy newborn infants were examined on the first, second, and third days of life and subsequently at six months and one year. All of these children were the products of a full-term pregnancy and an uncomplicated delivery. Infants with any sign of neurologic disorder or respiratory distress were excluded from the study.

During the first three days of life an assessment of ocular alignment and motility was determined. All infants were examined in the supine position when they were wide awake and alert. Although a careful record was kept of drugs received by the mothers before delivery and by the infants, there did not seem to be any correlation between any medications received and the supranuclear gaze disturbances seen. A flashlight was used to estimate any deviation of the corneal light reflex from the center of the pupil (Hirschberg test). Examination of both horizontal and vertical versions was done using oculovestibular stimuli (Doll's eye phenomenon). Visual fixation and following were evaluated by using the examiner's face as the fixation target. Examination of the external appearance of the eyes including pupillary light responses was also done. On at least one occasion the pupils were dilated with one drop each of cyclopentolate HCl 0.5% and phenylephrine (Neo-Synephrine) 2.5%. The examinations at six months and one year were similar and a more accurate attempt was made to identify any persistent ocular misalignment.

A pediatric neurologist initially examined all of the children in whom a supranuclear disturbance of gaze was identified and re-examined them at either age 6 months or 1 year. Infants who exhibited either skew deviation or tonic downward deviation of the eyes were

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examined by computed axial tomography of the brain. All neonates who showed opsoclonus were evaluated with electroretinography, visually evoked cotical responses, intravenous pyelography, and urinary measurement of vanillylmandelic acid and catecholamines. Examination of the cerebrospinal fluid was performed on some, but not all, of these infants.

Results

Five children showed transient downward deviation of the eyes in the neonatal period. This ocular motor disorder resolved within six months without any sequelae in all cases. The disorder is characterized by a tendency for both eyes to be tonically deviated downward at all times when the patient is awake, but the eyes usually return to the horizontal plane during sleep. Moreover, oculocephalic stimulation easily elicited a full range of elevation of the eyes. No eyelid retraction or pupillary abnormality was seen in these patients. Computed axial tomography of the brain did not reveal any evidence of hydrocephalus or focal brain stem disease in any of these infants.

Opsoclonus was seen in eight children. Because this disorder tended to be seen only intermittently other neonates may have exhibited this ocular movement abnormality at times other than when we were examining them. Opsoclonus seemed to be most noticeable just before feeding and sleeping. In three infants the opsoclonus regressed through a phase of ocular flutter before resolving completely. The ocular movements of six of these children were entirely normal by 1 month of age, and the other two developed normal ocular motor control by age 6 months. Electroretinography, visually evoked cortical responses, intravenous pyelography, and urinary levels of vanillylmandelic acid and catecholamines were normal for age in all these children.

Ocular skew deviation was seen in 22 neonates. There was no preference as to the hypertropic side; in 12 patients the right eye was higher and in ten the left eye was higher. The vertical deviation was accompanied by a horizontal disconjugate separation in seven children. Eleven of these children were considered small for their gestational age, but otherwise healthy. No other signs of brain stem dysfunction were seen in any of these children. In 15 of these infants the skew deviation had resolved by 3 days of life; in two others, by age 1 month. However, five of the children initially exhibiting a skew deviation in the neonatal period subsequently developed signs of a large angle esotropia with cross fixation thought to be typical of congenital esotropia. In all five of these children a horizontal component to the skew deviation had been seen. In two of the esotropic children the features of the nystagmus compensation syndrome were identified.[5] Computed axial tomography of the brain was normal in all of these neonates showing ocular skew deviation. In addition to the 35 infants in whom a transient supranuclear disturbance of gaze was noted 21 infants manifested a transient esotropia or exotropia during these neonatal examinations.

Discussion

In 1955, Lebensohn[2] described tonic downward deviation of the eyes in an infant who had sustained obstetric trauma at birth. Spontaneous recovery occurred by age 17 months. Similar cases have been detailed by Walsh and Hoyt,[3] and Daroff and Hoyt.[6] Characteristically, this deviation has been reported to be present at birth, less marked during sleep, and easily overcome when the head is passively flexed forward.[2,3,6] Retraction of the upper eyelids was reported by Lebensohn,[2] but these features have been less prominent, or absent in subsequent reports.[3,6]

In our study, five infants exhibited tonic downward deviation of the eyes. The eyes were constantly directed downward while the neonates were awake, but turned up during sleep. Eyelid retraction and pupillary irregularity were absent in our patients. None of our patients had suffered from any significant perinatal trauma or illness. One of our patients was an identical twin; the other twin did not exhibit any abnormal eye movements.

This ocular disorder superficially resembles the setting sun sign, a familiar accompaniment of hydrocephalus.[7–9] However, in the case of hydrocephalus, a supranuclear paresis of upward gaze is the essential feature of this periaqueductal disturbance. In contrast, neonates with tonic downward deviation of the eyes show normal upward movements during sleep and with oculocephalic maneuvers. Moreover, computed axial tomography did not reveal any sign of hydrocephalus or focal intracranial disease in any of the five neonates we studied.

Spontaneous tonic downward deviation of the eyes has been reported in other clinical settings including coma induced by some of the metabolic encephalopathies,[6,10] following a generalized seizure,[10] and in structural brain lesions frequently causing coma.[10] The classic eye position noted in thalamic hemorrhage and the ocular bobbing of massive pontine lesions are also commonly recognized examples of tonic downward ocular deviation.[6] Recently, the phenomenon of forced downward deviation of the eyes after oculovestibular testing in a comatose patient was reported to be indicative of a sedative-hypnotic drug overdose.[11]

The anatomic site and physiologic or biochemical nature of the underlying disturbance in neonates with tonic downward deviation of the eyes is unknown. Clearly, this abnormal eye movement is not a gaze paralysis of upward gaze because it resolves during sleep and can be overcome with oculocephalic testing. We suggest that it may represent a maturation delay in one of the reflex subsystems involved in upward gaze. However, we have no data to be more precise about the anatomic substrate responsible for this phenomenon. During the first year of life, the human infant matures from a state in which motor activity is largely reflex to one in which motions and postural reactions are mostly voluntary.[12] Integration of visual, auditory, vestibular, and proprioceptive stimuli with the ocular motor pathways is essential to achieve this maturation process and an error in any one of the involved systems could be responsible for this ocular movement disorder.

The term opsoclonus was first introduced by Orezechowski[13] to describe an unusual disturbance of ocular motility. It is characterized by irregular, chaotic, semiconjugate, rapid back and forth oscillations of the eyes in a horizontal, vertical, or oblique direction.[13] Opsoclonus may be continuous, even during sleep or coma, or it may only be evident during refixation saccadic movements. It is distinct from nystagmus in lacking the rhythmicity and regularity inherent to nystagmus.[14,15] Opsoclonus is seen in both children and adults, but is rarely seen in the newborn infant.[4,16]

In both children and adults, opsoclonus is most frequently associated with encephalitis.[14,15] A separate clinical entity in children has been described as infantile polymyoclonia in which abnormalities in the serum and cerebrospinal fluid immunoglobulins coupled with cerebrospinal fluid plasmocytosis indicates a disturbance of the immune system.[17] An important associative condition seen in some cases of opsoclonus in children is neuroblastoma.[18] We believe that the recognition of opsoclonus in a child with no cerebrospinal fluid evidence of encephalitis obligates the physician to a

thorough search for a neural crest tumor. Bienfang[16] reported five cases of neonatal opsoclonus. Three of these patients had significant mental and neurologic disturbances; two had severe visual loss from either optic nerve or retinal disease.

The eight neonates with opsoclonus examined by us in this study did not show any signs of encephalitis, neuroblastoma, diffuse neurologic damage, or severe visual loss. Electroretinography, visually evoked cortical responses, intravenous pyelography, and urinary levels of vanillylmandelic acid and catecholamines were normal in all of these patients. The eye movement disorder was self-limited and greatly resolved in the first week of life. In all cases, the ocular movements were normal by age 3 months. Recovery of normal ocular motility was often preceded by a state of ocular flutter. This agrees with the observations of Savino and Glaser[19] who postulate that ocular dysmetria, ocular flutter, and opsoclonus are a spectrum of disability of a single eye movement system.

The frequent association of opsoclonus with ataxia and other signs of cerebellar disease has been cited as evidence that opsoclonus is a manifestation of cerebellar dysfunction.[15,20] Pathologic studies support this thesis. Demyelination of the peridental region and Purkinje cell loss have been noted in cases of opsoclonus resulting as a remote manifestation of carcinoma in adults[20,21] and neuroblastoma in children.[22,23] Conversely, Orzechowski[13] in his original description of opsoclonus postulated that it was a phenomenon related to disease in the mesencephalon or basal ganglia. Cogan[15] reported a case of opsoclonus with lymphocytic infiltration in the hypothalamus, midbrain, and pons and concluded that a diffuse inflammatory process of the brain stem may be the pathologic basis of opsoclonus.

Zee and Robinson[24] have asserted that opsoclonus represents an abnormality of cells that inhibit saccades. Therefore, neonatal opsoclonus may occur as a result of delayed maturation and synaptic organization of these "pause" cells within the brain stem. However, pathologic confirmation of this proposal is unlikely because the prognosis for survival and normal development appears to be excellent in these infants.

Skew deviation is a term that refers to an acquired vertical divergence of the eyes caused by supranuclear dysfunction.[25] The degree of ocular separation may be constant or variable in different positions of gaze, and there may be an accompanying horizontal disconjugate separation.[26] It must be differentiated from intranuclear or neuromuscular causes of vertical divergence.

Keane[25] stated that

> the importance of a better understanding of skew is underscored by its clinical frequency and its possible relationship to comitant childhood strabismus.

However, we have been unable to find any previous report concerning neonatal skew deviation. Our study documents that it is a frequent transient ocular motility disturbance in healthy neonates. Additionally, in contrast to the neonates with tonic downward deviation or opsoclonus who recovered without any residual ocular motor disturbance, a significant number of newborns with skew deviation later developed signs of comitant horizontal strabismus.

Skew deviation is generally considered a poorly localizing sign of posterior fossa dysfunction.[25,26] In 1826 Henry Hertwig[27] made a surgical lesion in the brain stem of a cat, with the incision coming in laterally from a cerebellar hemisphere toward the midline of the medulla. This animal developed skew deviation, with the hypotropic eye ipsilateral to the lesion. Subsequently, experimental lesions in many areas of the brain stem and

cerebellum have been reported to produce skew.[25] Skew resulting from lesions at many brain stem sites indicates that vertical alignment must be diffusely represented in the brain stem. Most discussions of the cause of skew deviation have emphasized the possible role of tonic vestibulo-ocular regulation.[28] The hypothesis has been presented that skew results from damage to tonic otolithocular pathways.[25] Because five of the 22 patients with neonatal skew deviation later developed the features of congenital esotropia, we have initiated a study of the brain stem function of infants with congenital esotropia. Preliminary results (unpublished data) indicate that a significant subgroup shows abnormal auditory-evoked brain stem potentials.

The maturation of ocular motor systems is less well understood than that of the sensory systems. However, as clinical ophthalmologists continue to participate in the care of healthy and preterm neonates the need to detail these processes is self-evident. Our study has shown that transient supranuclear disturbances of gaze are common in healthy neonates. In the case of tonic downward deviation and opsoclonus, the ocular motor disturbance is self-limited and not a sign of significant systemic or neurologic disease. In contrast, although neonatal skew deviation spontaneously resolves in some cases, it appears to be a precursor of comitant horizontal strabismus. This observation has directed our attention to an evaluation of brain stem function in patients with congenital esotropia.

Summary

We examined 242 healthy neonates. Five developed transient tonic downward deviation of the eyes and eight showed any resultant visual, systemic, or neurologic abnormality. However, five of the 22 children with neonatal skew deviation developed a subsequent comitant horizontal strabismus. Although transient supranuclear disturbances of gaze are common in healthy neonates, skew deviation is a risk factor for development of horizontal strabismus.

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CEREBRAL BLINDNESS AND OCULOMOTOR NERVE PALSIES IN TOXOPLASMOSIS

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Loss of vision caused by retinochoroiditis is a well-documented complication of congenital ocular toxoplasmosis.[1,2] Because the use of immunosuppressive chemotherapy for neoplasia, collagen vascular disease, and organ transplantation has become prevalent, acquired toxoplasmosis of the brain[3,4] and eye[5,6] is being recognized with increasing frequency. This clinicopathologic report of two cases shows that toxoplasmosis can cause visual loss from involvement of cerebral visual pathways and that it can occur with oculomotor nerve palsies in immunosuppressed patients. These ophthalmic manifestations of central nervous system toxoplasmosis may appear as complications of the underlying systemic disease.

CASE REPORTS

Case 1—A 31-year-old man was admitted to the Toronto Western Hospital ten days after the onset of diplopia and left-sided blepharoptosis. Weakness of the right arm and leg occurred two days later. His medical history included glomerulonephritis at age 3 years, and hypertension since age 18 years. Chronic renal failure occurred when he was 23 years old and he received a cadaver renal transplant at age 25 years. Immunosuppressive therapy during the year before admission to the hospital consisted of 10 to 15 mg of prednisone daily and 50 to 75 mg of cyclophosphamide daily.

The visual acuity was 6/6 (20/20) in each eye but the patient had a congruous left inferior quadrantic visual field defect with a sloping margin. Results of ophthalmoscopy were normal and there were no signs of uveitis. He had a partial left third nerve palsy. The left pupil was 5 mm with impairment of both constriction and dilation, indicative of combined parasympathetic and sympathetic defects. There was a right central facial paresis and mild pyramidal weakness of the right arm and leg. His blood pressure was 160/100 mm Hg and he was afebrile. The results of the physical examination were otherwise normal.

Biochemical and hematologic values were normal except for mild thrombocytopenia. Two cerebrospinal fluid examinations showed mild increased protein concentrations (86 and 112 mg/100 ml) and mononuclear leukocytes were 8/mm^3 in one specimen. Cerebrospinal fluid glucose levels were normal and bacterial and fungal cultures were negative. Serum immunofluorescent antibody tests for toxoplasmosis (Wellcome reagents)[7] performed one year before hospital admission showed an IgG-immunofluorescent antibody test titer of 1:1,024 and a negative IgM-immunofluorescent antibody test titer. The IgG and IgM titers remained unchanged when tested one and two weeks after the onset of the third nerve palsy. A vertebral angiogram showed atherosclerotic dilation and ectasia (dolichomegaly) of the basilar artery and a left carotid angiogram was normal. Technetium brain scanning showed increased uptake in the right occipital lobe. A computed tomographic brain scan showed radiolucent areas in the right occipital lobe and deep in the left thalamus.

The patient was discharged to a convalescent hospital with a diagnosis of Weber's syndrome from midbrain infarction and right occipital lobe infarction caused by vertebrobasilar thromboembolism. The left oculomotor nerve palsy was complete. Blindness with intact afferent pupillary reflex activity ensued. The cerebral blindness was attributed to bilateral occipital lobe infarction from hypertensive atherosclerotic vascular disease of the vertebrobasilar circulation. Three months after the onset of the third nerve palsy the patient became obtunded and he was readmitted to the hospital where he became comatose and died six days later.

On pathologic examination the brain appeared

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grossly normal except for severe atherosclerotic changes in large cerebral vessels. Coronal sections of the formalin-fixed brain showed several irregular yellow-white lesions surrounded by gray softened zones in the brain stem and cerebrum. Destruction of the left cerebral peduncle and oculomotor nerve fascicle (Fig. 1, top left) explained the hemiparesis and third nerve palsy. The left sympathetic pupillary defect was attributed to a discrete lesion of the left medulla dorsal to the inferior olivary nucleus. Multiple lesions of the right occipital lobe accounted for the left homonymous visual field loss (Fig. 1, top right). Involvement of the left optic tract by a large lesion within the internal capsule and adjacent corpus striatum (Fig. 1, bottom left) caused the subsequent right homonymous field defect that culminated in blindness.

Histopathologic examination showed lesions of varying ages, some being recent and active, with acute coagulative neuronal necrosis and dense infiltration by acute and chronic inflammatory cells, and others showed collagenous encapsulation as evidence of chronicity and healing. Gliosis was most pronounced in the older lesions. In the acute lesions,

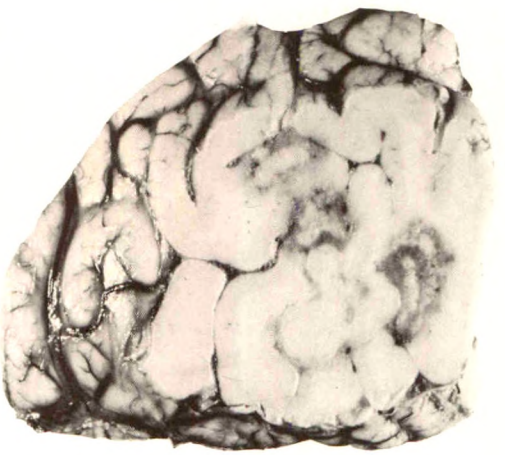

Fig. 1 (Wilson, Sharpe, and Deck). Case 1. Coronal sections of brain showing (top left) midbrain lesion that destroyed left cerebral peduncle and oculomotor nerve fascicle; top right, right occipital lobe lesions; bottom left, left internal capsule lesion involving subjacent optic tract.

Toxoplasma gondii organisms (Fig. 2, left) were present in both free (tachyzoite) and encysted (bradyzoite) forms. Extra- and intracellular free protozoa occurred in groups and as isolated organisms. The extracellular cysts had argyrophilic walls and contained PAS-positive storage material (Fig. 2, right). Despite the clinical profile of vascular disease, the infestation did not cause vasculitis. Although cerebral atherosclerosis was severe, none of the cerebral lesions had characteristics of infarcts. No evidence of toxoplasmosis was found in the transplanted kidney or in other organs.

Case 2—A 50-year-old woman was admitted to the hospital because of persistent fever complicating systemic lupus erythematosus. She had been taking 10 to 60 mg of prednisone daily in varying doses for six years. She complained of diplopia and physical examination showed a left sixth nerve palsy. There were no other ophthalmic or neurologic deficits. Lumbar puncture showed normal cerebrospinal fluid. Blood cultures were positive for *Listeria monocytogenes* and the patient was treated with appropriate antibiotics. The sixth nerve palsy was presumed to be a mononeuritis complication of the vasculitis; it resolved within several weeks. Her subsequent course was complicated by corticosteroid induced proximal myopathy and lumbar vertebral collapse. The prednisone dosage was reduced and chlorambucil therapy was begun.

One year after the left sixth nerve palsy occurred the patient was admitted again to the hospital with symptoms of cranial neuropathy involving the right trigeminal, glossopharyngeal, and vagal nerves. The cranial nerve palsies were attributed to systemic lupus erythematosus. Subsequently the patient had a left inferior homonymous quadrantanopia and right blepharoptosis and miosis were detected. Horner's syndrome in the right eye was followed by a right lower motor neuron seventh nerve palsy, left hemiparesis, and ataxia of the left arm and leg.

A brain scan showed increased radionucleotide uptake in the right occipital lobe. The cerebrospinal fluid examination showed mononuclear leukocytes of 10/mm^3 and red blood cell count of 299/mm^3, a protein concentration of 62 mg/100 ml, and a glucose value of 51 mg/100 ml. Sabin Feldman dye tests showed unchanging titers of 1:64,000 on three occasions during the development of the hemianopia and cranial nerve palsies. The IgM-immunofluorescent antibody test was 1:40 on three occasions. Four-vessel cerebral angiography was normal except for an avascular region in the right parieto-occipital area.

The patient was treated with 60 mg of prednisone daily for presumed cerebral and brain stem vascular complications of lupus erythematosus. During the next two weeks she had two cardiorespiratory arrests. The patient remained comatose and died three weeks after admission to the hospital.

Neuropathologic examination showed multifocal discrete cerebral and brain stem lesions. An area of coagulative necrotizing encephalitis of the right superior calcarine cortex explained the left inferior quadrantic visual field loss. Diffuse confluent lesions in the pons, medulla, and cerebellum accounted for the right trigeminal, glossopharyngeal, and vagal nerve palsies as well as the left hemiparesis and the ataxia. The previous left sixth nerve palsy was attributed to an older lesion bordering on the abducens nerve fascicle.

Microscopic examination of the grossly involved regions showed necrotizing encephalitis with inflammatory response consisting of lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. Free and encysted *T. gondii* organisms were evident within the regions of brain necrosis. Diffuse vasculitis was most pronounced adjacent to the toxoplasmosis lesions, suggesting that it represented an inflammatory response to the organism rather than the underlying lupus vasculitis.

Discussion

These cases show that visual sensory or motor system involvement can be promi-

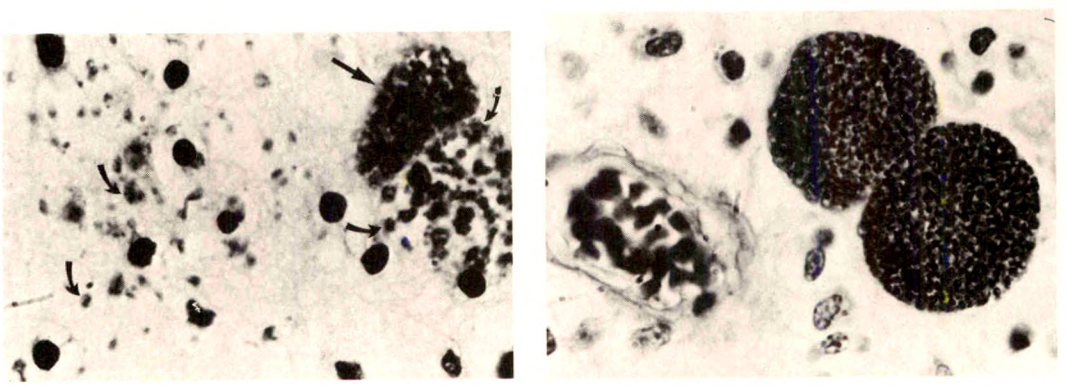

Fig. 2 (Wilson, Sharpe, and Deck). Case 1. Photomicrographs from margin of necrotic cerebral lesion showing (left) free *T. gondii* (curved arrows) and organisms within macrophage (straight arrow) (hematoxylin and eosin, ×1,000); right, cysts of bradyzoites (PAS, ×1,000).

nent in patients with central nervous system toxoplasmosis associated with therapeutic immunosuppression. Visual loss in congenital toxoplasmosis usually results from chorioretinitis.[1,2] This probably also is true in acquired toxoplasmosis.[5,6] Changes in the clear media of the eye associated with uveitis or optic nerve infiltration may also be responsible for impaired vision.[1] Both of our patients had involvement of visual radiation and occipital lobe that caused hemianopic visual loss. In one patient (Case 1) subsequent involvement of the contralateral optic tract culminated in cerebral blindness. Oculomotor nerve palsies were the manifesting signs in each case, a third nerve palsy in one and a sixth nerve palsy in the other. The ophthalmoplegia was caused by damage to the oculomotor and abducens nerve fascicles within the brain stem. Both patients had unilateral Horner's syndrome from involvement of the brain stem sympathetic nerve pathway.

Acquired toxoplasmosis of the brain may be secondary to immunosuppressive therapy or primary without other systemic disease.[4] The lack of ocular and intracranial evidence for congenital toxoplasmosis in our cases suggests they had an acquired form of the disease. Cerebral toxoplasmosis may indicate three primary clinical syndromes: diffuse encephalopathy; meningoencephalitis; and solitary or multifocal mass lesions.[3,4] The neuro-ophthalmic signs occurring in our patients show the brain stem, thalamic, and parieto-occipital involvement that frequently occurs in the focal form of toxoplasmosis.[3,4,8–10] Acquired toxoplasmosis in the adult may result from either recent exposure to the organisms or reactivation of dormant foci of this facultative protozoan pathogen.

Reduced immunity associated with intensive cranial radiotherapy, lymphoproliferative malignancy, or immunosuppressive chemotherapy may lead to activation of encysted cerebral *Toxoplasma*.[11] Frenkel, Nelson, and Arias-Stella[3] speculated that the brain is susceptible to activation of latent *Toxoplasma* infestation because cellular neural immune mechanisms are ineffective, whereas systemic cellular and humoral immunity remain effective. Ocular toxoplasmosis[5,6] in patients with impaired immune competence suggests that the eye, like the brain, is selectively vulnerable to activation of latent organisms. A high ratio of aqueous humor to serum antitoxoplasma IgG (Desmonts' coefficient) has been used to support the diagnosis of acquired toxoplasmosis of the eye.[6,12] The value of cerebrospinal fluid antibody titers in the diagnosis of toxoplasmosis of the brain has not been determined, and other cerebrospinal fluid factors are nonspecific. The primary changes are mononuclear pleocytosis and a moderately increased total protein.

Serologic testing indicates that some 10 to 70% of the general population has been exposed to toxoplasmosis and that the incidence of exposure increases with advancing age.[13] High IgM-immunofluorescent antibody test titers are considered indicative of recently acquired infection.[13,14] The negative IgM titer in Case 1 and the low titer in Case 2 provide evidence that the organism was acquired months or years before clinical signs of infection,[14] perhaps in childhood. The relatively high titers of the dye test and the IgG-immunofluorescent antibody test in our patients suggested activation of previously dormant foci of *T. gondii*. Failure of these titers to increase during serial observation was erroneously considered to be evidence against progressive infection.

In our patients the neuro-ophthalmic signs were mistaken for complications of the systemic disease. The multifocal deficits occurring in stepwise fashion

were initially attributed to hypertensive and atherosclerotic cerebrovascular disease in Case 1, and in Case 2 they were thought to signify lupus vasculitis. Signs may remit, as the abducens palsy in Case 2. Progression and resolution of multifocal signs might be mistaken for demyelinating disease. Multifocal leukoencephalopathy, *Cryptococcus neoformans*, and *L. monocytogenes* are other opportunistic infections that should be considered in the differential diagnosis of such neurologic deficits in patients with immune deficiency. Serologic criteria alone may be insufficient to establish the diagnosis of acquired toxoplasmosis.[14] If serologic tests are inconclusive, biopsy of focal areas of cerebral damage identified by radiologic contrast studies may be required to determine the cause of these neuro-ophthalmic complications of systemic disease. Our experience indicates that toxoplasmosis should be considered in immunosuppressed patients who have visual field loss or oculomotor nerve palsies. Prompt treatment with pyrimethamine and sulfadiazine is effective.[4] We are aware of only one fatal case[4] among patients with cerebral toxoplasmosis who received full therapeutic courses of these drugs.

Summary

We studied the clinicopathologic and neuro-ophthalmic manifestations of central nervous system toxoplasmosis in two patients who were being treated with immunosuppressive chemotherapy, one for renal transplantation and the other for systemic lupus erythematosis. Both patients had oculomotor nerve palsies and later developed visual loss from cerebral involvement. Multifocal central nervous system toxoplasmosis appeared as a complication of their systemic diseases.

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REACTION TO INTRAOCULAR PENETRATION OF BENTONITE

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Corneal foreign body injuries are a well-known occupational hazard to those working in the dental health field.[1,2] We describe a case of a severe anterior segment inflammatory reaction in a dental assistant which was attributed to bentonite, one of the components of Prophypaste, a compound used to clean teeth. Additionally, we report results of animal studies confirming the ocular toxicity of bentonite.

CASE REPORT

A 20-year-old dental assistant noted a foreign body sensation in her right eye while using a slow-speed drill to polish a patient's teeth with Prophypaste. She was not wearing spectacles. She immediately noticed decreased vision and photophobia and consulted her ophthalmologist who removed several opaque deposits superficially embedded in her right cornea within two hours after the injury. There was no evidence of corneal perforation or iritis. There was a residual superficial corneal infiltrate noted paracentrally, and her visual acuity was reduced to 6/21 (20/70). During the next few days, an anterior uveitis developed and was treated with topically administered 1% prednisolone acetate and 1% atropine. The iritis became so severe that on two occasions parenteral adrenocorticotrophin was given. Three weeks after the injury the eye had slowly improved; the medications were gradually tapered and the patient returned to work. Two days after the cessation of topically administered corticosteroids (one month after the foreign body injury) a severe anterior uveitis recurred and she was referred to us. Visual acuity in the right eye was hand motions at 1 foot. The conjunctiva was moderately injected. The cornea was edematous with a superficial, peripheral ringlike stromal infiltrate and a deep inferior stromal infiltrate (Fig. 1). A superficial opacity was noted at the site of the original injury. A retrocorneal abscess was present inferiorly. The anterior chamber was deep. A red reflex was present, but fundus detail could not be seen. There was no eyelid edema present. Intraocular pressure (IOP) was 15 mm Hg by applanation. Medical history was unremarkable except for a flulike episode with diarrhea approximately four days before admission. Results of initial physical examination including pelvic examination were unremarkable.

Initial laboratory studies showed normal chest x-ray, electrocardiogram, urinalysis, and orbital x-rays. Hemoglobin was 12.1 g/100 ml; white blood cell count was 10,100/mm^3 with 64% polymorphonuclear leukocytes, 10% band forms, 22% lymphocytes, 1% monocytes, 2% eosinophils, and 1% basophils. Electrolytes were normal except for potassium, which was 3.0 mEq/L. This was corrected within 24 hours by potassium supplementation administered orally. Despite intensive use of topically administered corticosteroids and cycloplegics, the anterior segment inflammation did not improve, and two days after admission an anterior chamber tap was performed. No organisms were seen but numerous polymorphonuclear leukocytes were noted on a Gram smear. Cultures were sterile for bacteria, yeast, fungi, and herpes simplex virus. Postoperatively, the infiltrate progressed and the patient developed a low-grade fever with an erythrocyte sedimentation rate of 78 mm/hr. Results of further examination were negative including liver function tests, protein electrophoresis, indirect fluorescein antibody for toxoplasmosis, VDRL, fluorescent-treponemal-antibody absorption (FTA-ABS) test, fluorescein antinuclear antibody (FANA), HLA-W27 typing, rheumatoid factor, and complement fixation test for histoplasmosis, blastomycosis, and coccidioidomycosis. A repeat erythrocyte sedimentation rate was 80 mm/hr two days later. A regimen of 650 mg (10 g) of aspirin four times daily and 60 mg of prednisone every morning was initiated. Although the retrocorneal abscess and edematous cornea with ringlike infiltrates persisted, the patient improved symptomatically and was discharged ten days after the anterior chamber tap.

However, within one week there was progression of the anterior segment inflammation and progression of the corneal edema, including bullae formation. The ring abscess in the corneal stroma had enlarged, as had the inferior retrocorneal abscess (Fig. 2). There was complete loss of red reflex and iris detail. No eyelid edema was present. A B-scan indicated no vitreous echoes or retinal disease. The eye became painful, visual acuity dropped to light perception with poor projection, and the IOP was 32 mm Hg by applanation.

Although the culture results from the first chamber tap remained sterile, our diagnosis was still

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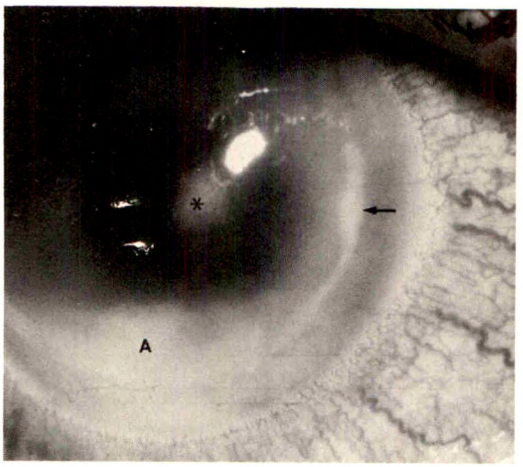

Fig. 1 (Austin and Doughman). Initial appearance of right eye. Note nebular central corneal scar (asterisk), ringlike corneal infiltrate (arrow), and inferior retrocorneal abscess (A). Corrected visual acuity, hand motions at one foot.

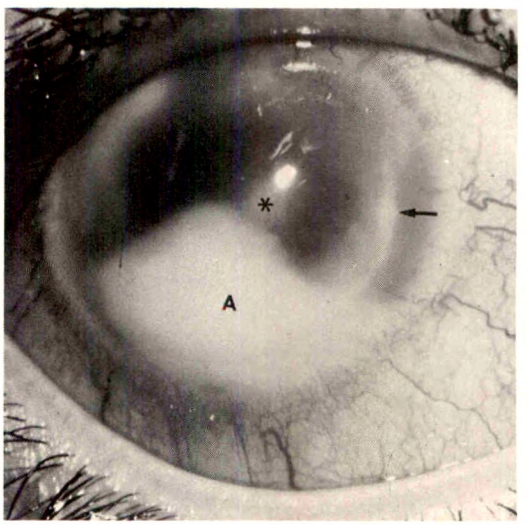

Fig. 2 (Austin and Doughman). Right eye, Appearance of anterior segment two weeks later. Note enlargement of ring abscess (arrow) of the corneal stroma and retrocorneal abscess (A). Visual acuity, light projection (asterisk designates corneal scar).

infectious endophthalmitis. Under general anesthesia, anterior chamber and vitreous aspirations were performed. The anterior chamber abscess was viscous and could not be completely removed. Vitreous aspiration showed clear fluid with a few polymorphonuclear leukocytes present and no organisms seen on Gram stains. Gram staining of the anterior chamber material was also negative for organisms. We suspected the presence of an anterior chamber foreign body and removed as much of the retrocorneal abscess as possible. Potassium hydroxide examination of the anterior chamber aspirate showed 1-μ round nonbirefringent refractile bodies, suggesting the presence of a mineral type foreign body. Postoperatively, the patient was given topically administered gentamicin, dexamethasone, and 1% atropine as well as systemically administered indomethacin. Additionally, penicillin was administered intravenously and orally because of the possibility that a fastidious mouth organism missed on the cultures may have been present. As in the first anterior chamber taps, all viral, fungal, and bacterial cultures were negative. The postoperative course was one of slow but progressive improvement (Fig. 3). One month postoperatively, her visual acuity pinholed to 6/18 (20/60). Four months postoperatively, the anterior chamber was clear, the cornea markedly improved, and visual acuity with refraction was 6/12 (20/40). The erythrocyte sedimentation rate one month postoperatively was 6 mm/hr and has remained normal since that time. Her most recent examination, 24 months after injury, showed posterior synechiae to the lens inferiorly with some subtle anterior cortical lens opacities. However, the anterior chamber and cornea were clear and her corrected visual acuity was 6/6 (20/20) (Fig. 4).

Material and Methods

The results obtained from the anterior chamber tap prompted toxicity studies with rabbits. We used Prophypaste as

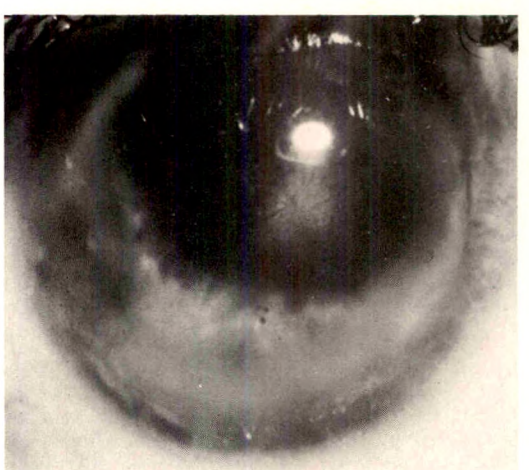

Fig. 3 (Austin and Doughman). One month postoperative. Note the marked improvement in inflammatory signs and absence of the retrocorneal abscess.

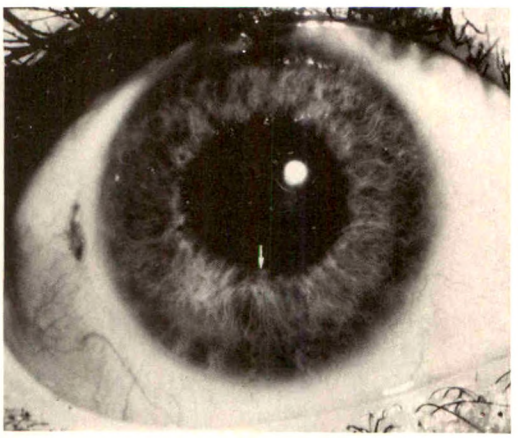

Fig. 4 (Austin and Doughman). Right eye 24 months after injury. Posterior synechiae (arrow) to the lens inferiorly is present. Corrected visual acuity is 6/6 (20/20).

well as its components: bentonite, gum tragacanth, and trypsin. These components are similar in size microscopically to the material found in the anterior chamber tap.

Six adult New Zealand rabbits were used for each compound studied. Preparations of Prophypaste, bentonite, tragacanth, trypsin, and sterile water were injected either intralamellarly or directly into the anterior chamber in concentrations ranging from 1 mg/ml to 5 mg/ml in a 0.1-ml volume. Histologic sections were obtained when indicated.

There was no significant reaction in six eyes that received Prophypaste, regardless of where injected. Likewise, there was no reaction with sterile water, tragacanth, or combinations of tragacanth and bentonite. Trypsin injected into the anterior chamber caused no reaction although in all six corneas intralamellar injection caused necrosis and perforation similar to that previously described.[3]

With bentonite, severe iritis was noted after its injection into the anterior chamber, but no corneal or retrocorneal reaction was noted grossly or histologically. In five of six eyes, where solutions of bentonite were injected intralamellarly, widespread corneal infiltrates and retrocorneal membranes were evident within two to five days. In the one eye that had no reaction, only 0.1 ml of 0.25 mg/ml was injected. Some of the eyes showed a striking similarity of clinical appearance to that of the patient (Figs. 5 and 6). Anterior chamber taps of these eyes showed viscous mucopurulent material requiring forceps for removal in some cases. Microscopic analysis of the taps showed particles similar in size to those seen in the patient. Histologic sections showed pseudoeosinophils, retrocorneal membranes, and fibrovascular membranes in the anterior segments. Under polarized light, bentonite is highly birefringent and this was noted at the injection sites as well. However, the retrocorneal masses that developed after bentonite injury showed no birefringent material.

Discussion

We believe the clinical course, once the anterior chamber was evacuated, and

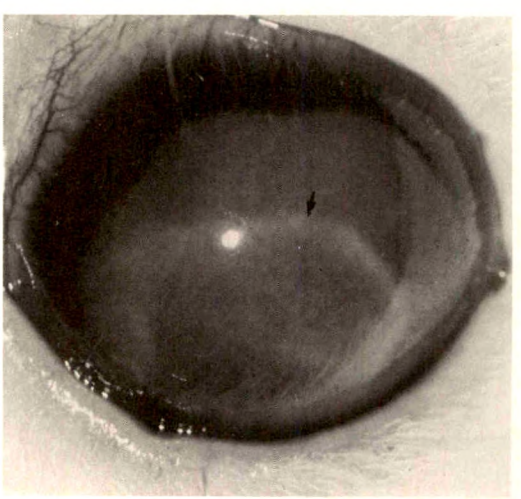

Fig. 5 (Austin and Doughman). Ring infiltrate (arrow) noted in one cornea in rabbit eye injected intralamellarly with bentonite.

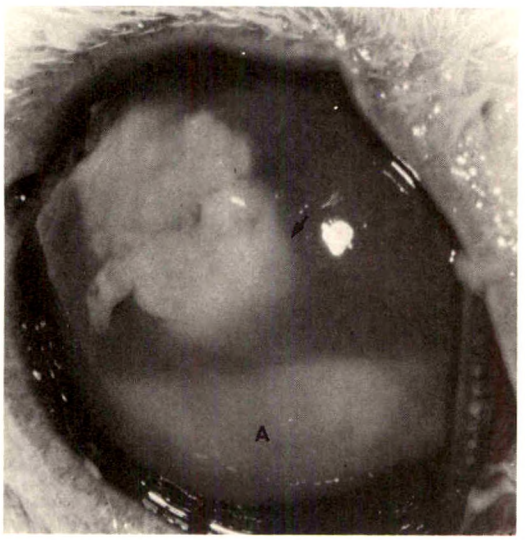

Fig. 6 (Austin and Doughman). Corneal infiltrate (arrow) and retrocorneal abscess (A) in one rabbit after injection with bentonite.

the similarity of the disease produced in the animal models after injection of bentonite is convincing evidence that bentonite was the agent in this case. However, there are unusual aspects of the case that leave some questions unanswered.

The delayed clinical manifestations are hard to explain. Possibly the corticosteroid therapy suppressed the reaction that only became manifest on the cessation of the corticosteroids one month after injury. There may also have been slow migration of the foreign material into the patient's anterior chamber that accounted for the time delay. The use of a slow-speed drill would militate against initial intraocular penetration.

The data for the animal model are also hard to interpret. Direct inoculation of bentonite into the anterior chamber created only a severe anterior iritis, not keratitis, or an inflammatory retrocorneal abscess. However, intralamellar inoculation into the cornea created a clinical appearance in the animal eye similar to that in the patient's eye including a retrocorneal abscess that contained refractile round nonbirefringent crystalline material similar to that found in the patient. This would seem to indicate that migration of bentonite from the cornea into the anterior chamber occurred in the rabbits. This supports our suspicion that bentonite migrated into the anterior chamber in the patient. In both the rabbit and the patient, we cannot explain the loss of birefringency of the material in the anterior chamber. Additionally, there is a much more severe anterior segment inflammatory response to bentonite in the cornea than in the anterior chamber. The rapid development of the clinical appearance in the animal as opposed to the patient could be explained on the basis that no corticosteroids were used to suppress the reaction in the animal. Species difference could also account for the time delay differences between the human and the animal results. However, why bentonite seems more virulent when injected into the cornea as opposed to the anterior chamber is not clear from our data. Neither can we explain why Prophypaste that contains bentonite caused no reaction. Perhaps the concentration of bentonite in the Prophypaste was too low to be toxic to the animals.

The patient had a repeatedly increased erythrocyte sedimentation rate of 80 and 78 mm, as well as a low grade fever with mild increase of her white blood cell count suggesting a systemic toxicity from this compound. This was substantiated by the normal results in the complete medical examination and because the erythrocyte sedimentation rate returned to normal again after the anterior chamber was evacuated. If this is true, bentonite is virulent in the eye or at least it was in this patient. None of the animals became ill, however.

Our animal experiments incriminate

bentonite for the following reasons: Microscopically, it is similar in size to the particles identified on slides from the initial anterior chamber aspirant from the patient. The lack of birefringence is consistent with the lack of birefringence in the anterior chamber tap in the patient and the rabbits. Finally, bentonite was the only component of Prophypaste that produced severe anterior chamber reaction with injection intralamellarly in experimental animals, whereas the other components of Prophypaste, similar in size to bentonite, caused no reaction. Possibly fragments of the rubber cup used to apply the Prophypaste could also have been responsible for the severe ocular reaction. We cannot absolutely state that bentonite was the cause, because we did not test this material.

A complete review of the published dental and ophthalmic reports failed to identify bentonite, a dehydrating agent composed of colloidal aluminum silicate, as a potentially harmful agent. Grant[3] as well as Goodman and Gillman[4] reported no adverse ocular reactions from this material. The Food and Drug Administration and the National Institute of Occupational Safety and Health have no reports of ocular complications secondary to bentonite (personal communications, January 1978). Talc is a closely related compound, that is, magnesium silicate. It has been reported to cause hypopyon in rabbits[5] and glaucoma in monkeys.[6] Recent articles in dental journals suggest that all patients, as well as dental professionals, should wear eye protection during the dental examination and procedures.[1,7,8]

Summary

A 20-year-old dental assistant had a severe case of anterior segment inflammation believed to be caused by bentonite, a component of Prophypaste. The patient's clinical course as well as animal studies, implicated bentonite as the offending agent.

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HISTOLOGIC AND IMMUNOHISTOLOGIC COMPARISON OF MAIN AND ACCESSORY LACRIMAL TISSUE

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The presumed sources of the watery middle layer of human tears are the main lacrimal gland (orbital and palpebral lobes) and the accessory glands of Krause and Wolfring.[1] Although these glands have a common embryologic origin and similar histologic structures (as noted by early anatomists),[2] the concept has evolved of differential secretion of unstimulated (baseline) tears and tears stimulated by irritation or emotion (reflex tears).[3] According to this theory, the accessory lacrimal glands provide the basic watery layer of unstimulated tears and the main lacrimal gland is the source of stimulated tears.

Jordan and Baum[4] reported that tear flow is increased by stimulation of the cilia and the eyelid margin, and suggested that all tear secretion may represent a reflex response to ambient ocular stimulation. This implies that baseline and reflex tears may have a common anatomic origin. With this hypothesis and the common embryologic origin and similar histologic structures in mind, we have examined main and accessory lacrimal tissues from autopsy exenterations by several histologic and immunohistologic techniques to investigate their similarities and differences in structure and secretory product.

Although the light-microscopic structure of accessory lacrimal tissue (which constitutes 10% of all lacrimal tissues) has been known since the time of Krause and Wolfring, only an occasional micrograph showing hematoxylin-and-eosin staining has been published. To the best of our knowledge, this is the first comprehensive histologic study of accessory lacrimal tissue.

MATERIAL AND METHODS

Tissue specimens — Main lacrimal glands were excised from 11 autopsy exenterations; superior forniceal and supratarsal conjunctivas containing accessory lacrimal tissue were also excised from five of these eyes. Additional lacrimal tissue was obtained by biopsy from three patients undergoing orbitotomy. Tables 1 and 2 give details on the specimens. No history of ocular disease in any of the autopsy cases was evident. Specimens were processed for routine light microscopy, 1-μ section light microscopy, and immunofluorescence microscopy.

Tissues designated for immunofluorescence studies were fixed in a solution of 19 parts absolute alcohol to one part glacial acetic acid at room temperature for 48 hours, by a modified version of a technique described by Wolman and Behar.[5] The tissue was then further dehydrated, embedded in paraffin, and cut into 4-μ sections. For indirect immunofluorescence study, deparaffinized tissue sections were incubated in a moist chamber with specific unconjugated antisera diluted 1:10 in 0.1M phosphate-buffered saline (pH 7.2) for 15 minutes, washed, and then incubated

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TABLE 1

DATA ON SOURCES OF AUTOPSY SPECIMENS

Lacrimal Tissue	Donor's Age (yrs)	Cause of Death	Postmortem Hours Before Exenteration
Main and accessory	72	Pancreatic cancer	20
Main and accessory	67	Metastatic cancer	15
Main and accessory	70	Pulmonary cancer	48
Main and accessory	65	Kidney failure	9
Main and accessory	52	Esophageal cancer	7
Main	67	Metastatic cancer	15
Main	67	Pneumonia	23
Main	59	Cardiac arrest	120
Main	54	Hepatic cirrhosis	22
Main	73	Progressive supranuclear palsy	22
Main	65	Pulmonary edema	31

with fluorescein-conjugated antisera to the first layer (diluted 1:40 in phosphate-buffered saline). Sections were again washed in phosphate-buffered saline. Control sections were made by substituting unconjugated serum gamma globulin for the antisera in the first incubation. For direct immunofluorescence study, tissue sections were incubated with fluorochrome-conjugated antiserum diluted 1:10 in 0.1M phosphate-buffered saline for 15 minutes, then washed for 15 minutes, and then washed in phosphate-buffered saline.

Tissues designated for 1-μ section light microscopy were fixed for three hours in a solution of 2% paraformaldehyde, 2.5% glutaraldehyde, and 0.025% $CaCl_2$ in 0.1M cacodylate buffer (pH 7.4). The fixative was then replaced with cold 0.1M cacodylate buffer (pH 7.4) containing 10% sucrose. The tissues were postfixed in osmium tetroxide, dehydrated in ethanol, and embedded in Epon. Sections 1 μ thick were cut and stained with alkaline Giemsa in 2% sodium borate.

TABLE 2

DATA ON SOURCES OF BIOPSY SPECIMENS

Lacrimal Tissue	Donor's Age (yrs)	Reason for Orbitotomy
Main	30	Epibulbar aneurysm
Main	35	Thyroid exophthalmos
Main	31	Thyroid exophthalmos

Tissues designated for routine light microscopy were fixed in neutral buffered formalin at room temperature for 48 hours, embedded in paraffin, cut into 4-μ sections, and stained with hematoxylin and eosin and PAS.

Antisera and their characterization—Monospecific rabbit antisera to human IgG, IgA, and IgM were one-line-specific by Ouchterlony analysis against normal human serum. Monospecific rabbit antiserum to human IgD, rabbit antiserum to human IgE, and rabbit antisera to human lactoferrin were one-line-specific by Ouchterlony analysis against colostrum and tears.

Tetramethyl rhodamine isothiocyanate-conjugated goat antihuman secretory component, fluorescein isothiocyanate-conjugated rabbit antihuman secretory component, and unconjugated rabbit antihuman secretory component were one-line-specific against colostrum and tears and identical by Ouchterlony analysis. Rabbit antihuman lysozyme

antisera were one-line-specific and identical by Ouchterlony analysis. Fluoresceinated goat antirabbit IgG was one-line-specific against normal serum. All antisera and their controls were used as the gamma globulin fraction.

Sections were examined with a Zeiss fluorescence microscope with an HBO 200-W high-pressure mercury vapor lamp, UG 5 excitor filter, and a 410-nm barrier filter for FITC and a 580-nm excitation filter with a 650-nm barrier filter for TRIC. Photographs for both fluorescein and rhodamine fluorescence were taken; fluorescein with the observation filter combination, rhodamine with the BG12 excitor filter and 530-nm barrier filter combination. Ektachrome ASA 200 and ASA 400 color films were used.

Results

All main and accessory lacrimal tissues examined were histologically similar. Hematoxylin-and-eosin staining showed that both main and accessory lacrimal glands had a tubuloacinar organization, with connective-tissue interstitium infiltrated with plasma cells and lymphocytes (Fig. 1). The small excretory ducts were lined by a single layer of cuboidal cells; the larger ducts had a multilayered epithelium. Both main and accessory lacrimal glands had PAS-positive granules in the apices of 50 to 75% of acinar cells, but not in the ductular epithelium (Fig. 2).

Alkaline-Giemsa staining of 1-μ sections showed similar structure of main and accessory lacrimal glands (Fig. 3). Acinar epithelial cells were conical, with broad bases and narrow microvilli-filled apices. Acinar cells contained secretory granules (primarily in the apical two thirds of the cell) and many lipid droplets. Ductular cells lacked secretory granules. Acini and ducts contained myoepithelial cells sandwiched between the base of the epithelial cells and the basement membrane (Fig. 3).

All immunohistologic results were also similar for main and accessory lacrimal glands. Immunofluorescent staining for immunoglobulins confirmed a previous observation[6] by showing strong interstitial and plasma-cell staining for IgG and IgA. Immunoglobulin IgD was seen in many interstitial plasma cells, and there was weak interstitial and plasma-cell staining for IgE and IgM.

Immunofluorescent staining for secretory component showed an identical staining pattern for both main and accessory lacrimal tissues (Fig. 4). Approximately 75% of acinar cells stained faintly

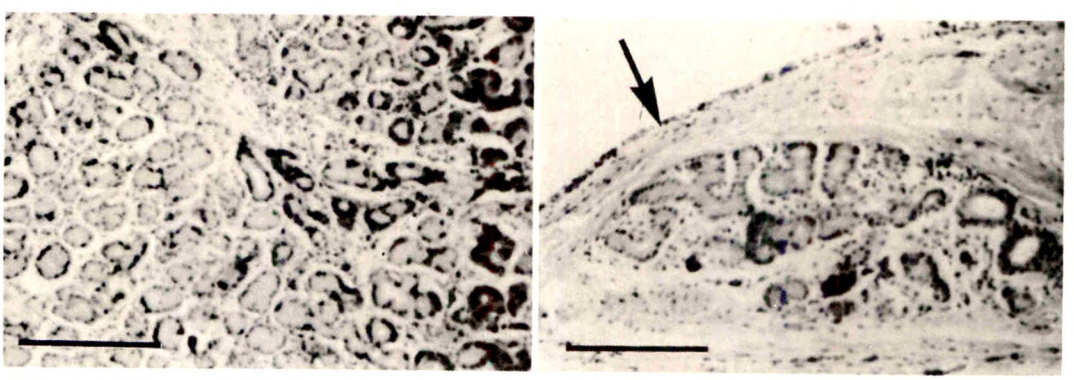

Fig. 1 (Gillette and associates). Main (left) and accessory (right) lacrimal glands, showing tubuloacinar organization. Conjunctival epithelium (arrow) is seen adjacent to the accessory lacrimal gland (hematoxylin and eosin, ×180; bar gauge = 100 μ).

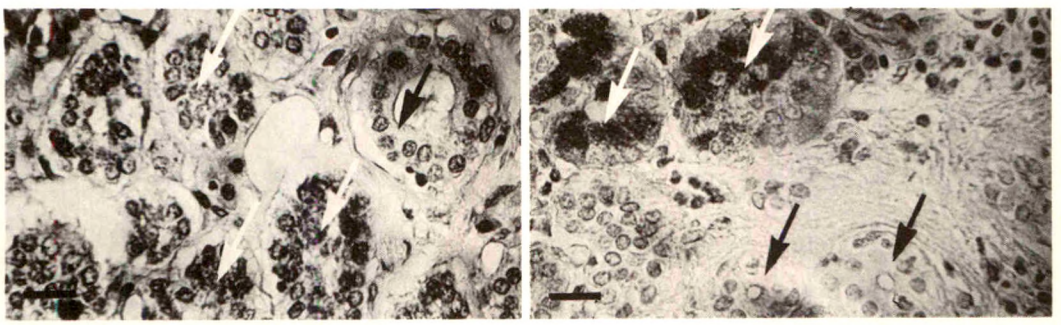

Fig. 2 (Gillette and associates). Main (left) and accessory (right) lacrimal glands, showing PAS-positive granules in the apices of acinar cells (white arrows) and the absence of such granules in the tubular epithelium (black arrows) (PAS, ×740; bar gauge = 10 μ).

for secretory component; about 5% stained brightly. There was bright staining of most of the epithelial cells of 30% of ductules.

Immunofluorescent staining for lactoferrin also was identical for main and accessory lacrimal tissue (Fig. 5). Approximately 90% of acinar cells stained brightly for lactoferrin; ductular epithelium was negative for lactoferrin.

The fluorescent-staining pattern for lysozyme was similar for both main and accessory lacrimal glands (Fig. 6). Both types of tissues showed staining for lysozyme in 30 to 50% of acinar and ductular epithelial cells. The staining was granular in character and localized to the apices of the cells. Positive cells tended to be grouped.

Discussion

The concept of differential secretion of tears rests largely on the lack of autonomic innervation of accessory lacrimal glands.[7,8] Although autonomic nerve terminals have been seen in the main lacrimal gland by electron microscopy,[8] the presence or absence of such terminals in the accessory lacrimal glands have not been studied. Ruskell[9] stated that "the rich innervation of duct and terminal tubule cells was largely related to the abundant myoepithelial cells" and found that the main lacrimal terminals were

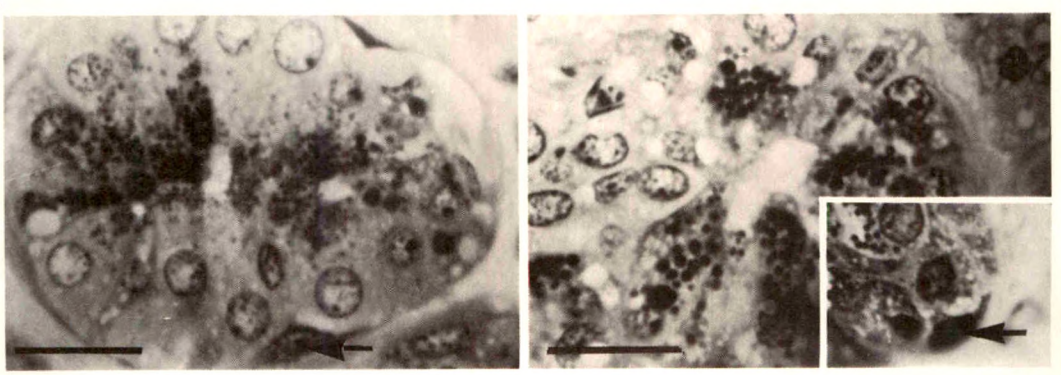

Fig. 3 (Gillette and associates). Main (left) and accessory (right) lacrimal glands, showing secretory granules in epithelial and acinar cells and (inset) peripheral myoepithelial cells (arrows) (alkaline Giemsa, ×1,840; bar gauge = 10 μ).

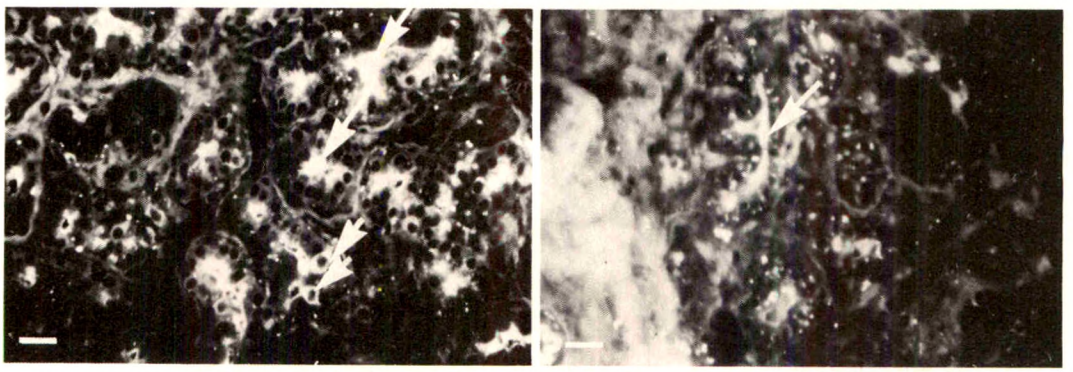

Fig. 4 (Gillette and associates). Main (left) and accessory (right) lacrimal glands, showing secretory component in acinar cells and in the tubular lumen (arrows) (fluorescein isothiocyanate-labeled goat antihuman secretory component, × 460; bar gauge = 10 μ).

exclusively parasympathetic. The presence of myoepithelial cells in accessory lacrimal glands probably indicates comparable autonomic innervation of accessory lacrimal tissue. The presence of such innervation requires histochemical and electron microscopic confirmation.

Immunologically, accessory lacrimal and main lacrimal gland tissue appear to be equivalent. Allansmith and associates[6] have shown that the number of plasma cells of the main and accessory lacrimal glands are about the same. It was our impression during the present study that the relative distribution of plasma-cell immunoglobulin type in accessory lacrimal glands is equivalent to that previously shown for the main lacrimal gland[10] and that the prominence of IgD plasma cells in accessory lacrimal gland tissue is consistent with that reported for the main lacrimal gland tissue.[11]

Additionally, secretory component, an integral part of the secretory IgA immunoglobulin found in human tears and previously shown to be present in lacrimal tissue,[10] is distributed identically in accessory and main lacrimal tissue.

The similar immunofluorescent-staining patterns for lactoferrin and lysozyme indicate comparable synthetic activities for main and accessory lacrimal tissue. In

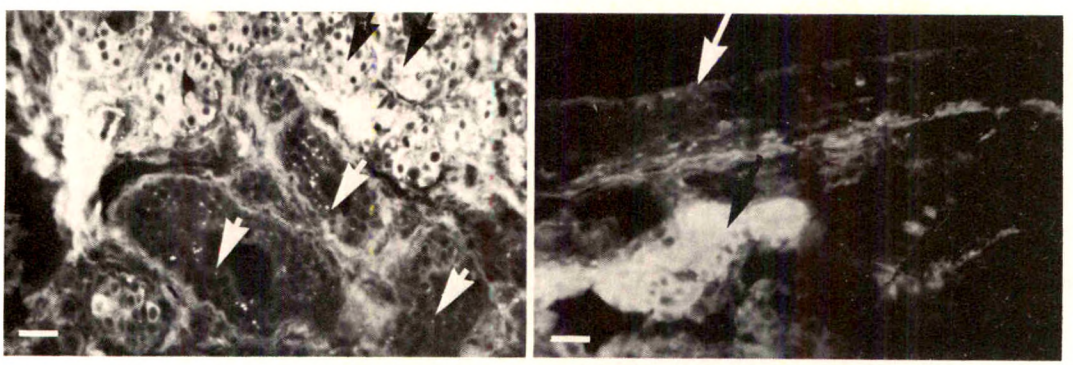

Fig. 5 (Gillette and associates). Main (left) and accessory (right) lacrimal glands, showing positive staining for lactoferrin in acinar epithelial cells (black arrows) and no staining in ductular epithelial cells. No staining is present in the epithelium of the ductules (white arrowheads). Conjunctival epithelium (white arrow) is seen adjacent to the accessory lacrimal gland (fluorescein isothiocyanate-labeled rabbit antihuman lactoferrin antiserum, ×400; bar gauge = 10 μ).

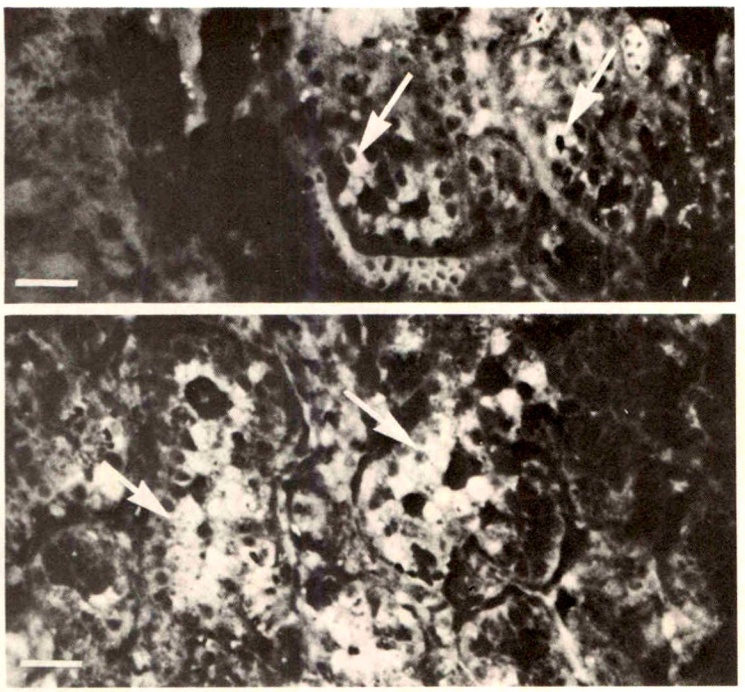

Fig. 6 (Gillette and associates). Main (top) and accessory (bottom) lacrimal glands, showing lysozyme localized to the apices of the cells (arrows) fluorescein isothiocyanate-labeled rabbit antihuman-lysozyme antisera, ×740; bar gauge = 10 μ.

1958, McEwen, Kimura, and Feeney[12] stated that "when the [main] lacrimal gland is removed by surgery, lysozyme . . . disappear [s] from the tear pattern," suggesting that lysozyme was not made by accessory lacrimal tissue. Our data indicate that lysozyme is produced in the accessory glands as well. The implication for disorders associated with decreased tear lysozyme content, such as keratoconjunctivitis sicca,[13] may be that the accessory glands are involved in the same pathologic process as the main gland.

Summary

Main and accessory lacrimal tissues from autopsy and biopsy specimens were compared histologically and immunohistologically. Formaldehyde-fixed, paraffin-embedded specimens were studied by light microscopy with hematoxylin-and-eosin and PAS staining. Glutaraldehyde-fixed, Epon-embedded specimens were sectioned at 1 μ, stained with alkaline Giemsa, and studied by light microscopy. Specimens fixed in a solution of alcohol and acetic acid were stained by immunofluorescence techniques for lactoferrin, lysozyme, secretory component, and the immunoglobulins IgG, IgA, IgM, IgD, and IgE.

The main and the accessory lacrimal tissues were identical histologically and had identical distributions of secretory products and immunoglobulin-containing plasma cells. The finding of myoepithelial cells in 1-μ sections of accessory lacrimal tissue indicates autonomic innervation in that tissue. This finding, in conjunction with the identical immunohistology, indicates a common source for unstimulated and stimulated tears.

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AUTOMATED SUPRATHRESHOLD STATIC PERIMETRY

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Automated perimetry is rapidly becoming a popular method of performing quantitative visual field testing.[1–10] Theoretically, automated testing should offer many advantages over manual perimetry, including reductions in the time and cost of performing visual field tests, standardization of test conditions, electronic monitoring of eye movements, and administration of visual field examinations by personnel with little or no training in perimetry. The practical value of automated perimetry, however, depends on its ability to detect and monitor accurately the progression or regression of visual field defects produced by various visual disorders. It is therefore necessary to perform careful comparison studies of manual and automated perimetric techniques to determine the relative performance capabilities of each method.

We have recently conducted preliminary studies comparing the Fieldmaster Model 101-PR automated perimeter to manual kinetic testing with the Goldmann perimeter.[1,2] The results indicated that automated testing with the Fieldmaster showed a high detection rate (correctly reporting the presence of a visual field defect) and a low false alarm rate (incorrectly reporting a visual field defect when none is present) in comparison to manual kinetic testing. We concluded that with the use of proper test conditions, the Fieldmaster Model 101-PR is an excellent screening device for detecting visual field defects, although detailed assessment of visual field loss (size, shape, depth, and other characteristics) is rather limited.

The purpose of the present study is to extend our comparisons of manual and automated perimetry to larger populations of various ocular disease categories, and to evaluate the ability of the Fieldmaster to monitor progression or regression of visual field defects.

MATERIAL AND METHODS

Automated and manual perimetry was performed for 1,019 eyes of 536 patients (ages 5 to 85 years) seen in our eye clinic. A description of the number of eyes in each ocular disease category, the number of eyes with visual field defects, and other pertinent information is provided in Table 1.

Thorough descriptions of the equipment and techniques used in this study have been presented previously.[1,2] Basically, the Fieldmaster Model 101-PR (Fig. 1) consists of a uniformly illuminated white hemisphere of 30 cm radius, with 99 holes placed at selected locations in the visual field (Fig. 2). Within each hole, fiberoptic elements provide the target illumination from a single tungsten light source. Each spot lights up according to a random sequence, the patient depresses a button every time a target is seen, and the location of each response is recorded on heat-sensitive paper. This test procedure is conceptually similar to the manual glaucoma visual field screening technique developed by Armaly[11,12] and modified by Rock,

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TABLE 1

DETECTION OF VISUAL FIELD DEFECTS BY AUTOMATED PERIMETRY (FIELDMASTER) AND MANUAL KINETIC PERIMETRY (GOLDMANN)

Patient Category	No. of Eyes	No. of Defects	Automated (Fieldmaster) Detection Rate (%)	Automated (Fieldmaster) False Alarm Rate (%)	Manual Kinetic (Goldmann) Detection Rate (%)	Manual Kinetic (Goldmann) False Alarm Rate (%)
Normal	310	0	N.A.	4.8	N.A.	N.A.
Retinal disease	68	56	96.4	4.4	100.0	0.0
Glaucoma and ocular hypertension	226	101	90.0	6.2	95.0	0.0
Optic nerve disease	147	121	100.0	2.7	86.0	0.0
Postchiasmal disorders	80	78	96.2	0.0	100.0	0.0
Miscellaneous disorders	178	80	97.5	6.7	100.0	0.6
Total population	1,019	436	96.1	4.7	97.9	0.3

Drance, and Morgan. [13,14] The procedure is generally referred to as suprathreshold static perimetry.

Background and target luminances of the Fieldmaster are continuously monitored by calibrated photocells. Accurate fixation is checked by an eye monitor that compares reflections from the patient's iris and cornea to an initial baseline value. Changes in fixation elicit a warning tone and halt the program until proper fixation is resumed. The Fieldmaster's control panel provides adjustments for background luminance (range, 1 to 45 asb), target luminance (range, 5 to 10,000 asb), target exposure duration (range, 0.2 to 3.6 seconds), time interval between successive presentations (range, 0.3 to 3.7 seconds), stimulus color (white, red, green, yellow, blue), and selection of test programs (full field, central 30-degree field only, periphery only). Additional features include an adjustable head-and-chin rest, translucent occluders for the nontested eye, and a lens holder for providing appropriate refractive corrections for the central 30-degree visual field test. The Model 101-PR version of the Fieldmaster also performs an automatic recheck of all missed test spots, a procedure that is necessary to maintain a low false alarm rate.[1,2] Manual selection and presentation of individual target locations can also be performed.

Table 2 presents a summary of optimal test procedures for the Fieldmaster Model 101-PR, based upon previous investigations.[1,2] Background luminance was adjusted to 31.5 asb, the standard background level used for the Goldmann perimeter. A stimulus duration of 0.8 seconds was used, with a time interval of 0.9 seconds between stimulus presentations. To avoid a rhythmic test sequence, 25% of the interstimulus intervals were 1.2 times longer than the selected value, and another 25% were increased by a factor of 2.0. Stimulus luminances of 635 and 200 asb were used for the two test runs described in Table 2. The Fieldmaster meter readings are lower than actual stimulus luminances by a constant factor of 4.7. Therefore, a meter reading of 135 produces a stimulus luminance of 635 asb, and a stimulus luminance of 200 asb is produced by a meter reading of 44. In our preliminary study of the Fieldmaster Model 101-PR, the conversion factor was not reported.[1] This conversion factor of

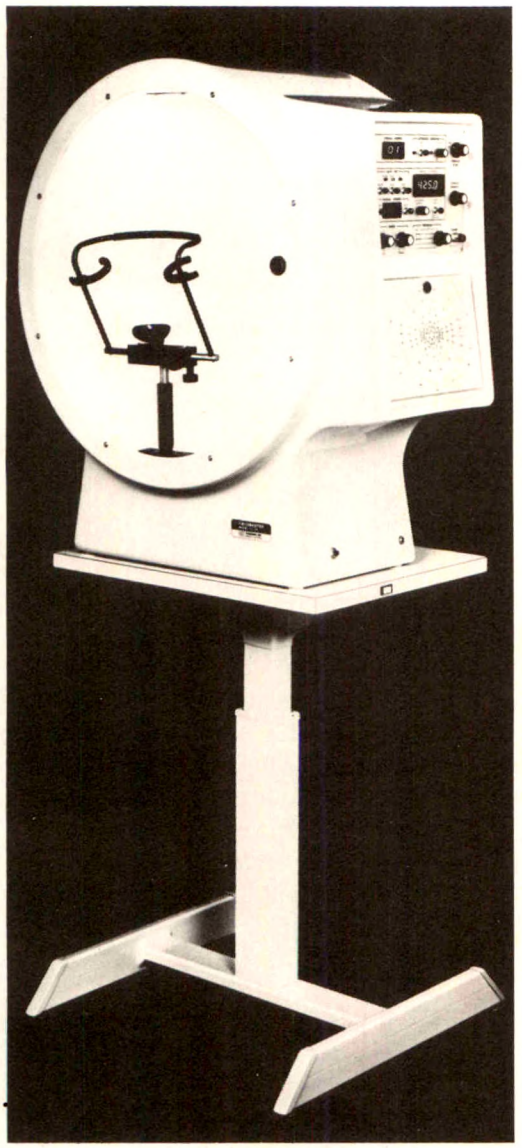


Fig. 1 (Johnson and Keltner). Photograph of the Fieldmaster Model 101-PR.

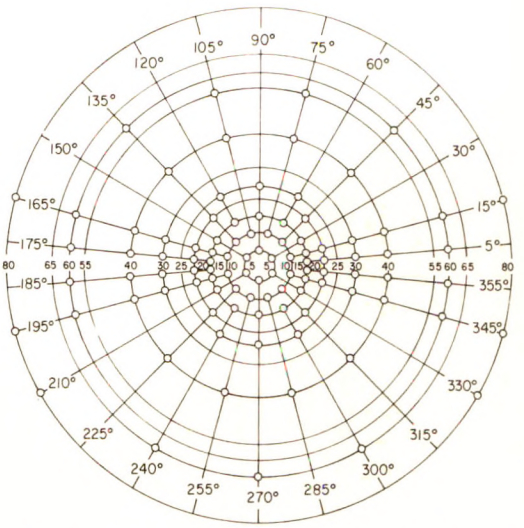


Fig. 2 (Johnson and Keltner). Distribution of visual field locations examined by the Fieldmaster Model 101-PR.

4.7 pertains only to stimulus luminance meter readings; background luminance meter readings are displayed in actual apostilb (asb) values.

Each Fieldmaster visual field evaluation in this study consisted of a minimum of two tests: (1) a full visual field examination for the 635-asb stimulus luminance (meter reading, 135); and (2) a central 30-degree visual field examination with an optimal lens correction, using the 200-asb stimulus luminance (meter reading, 44). Empirically, the 635-asb stimulus approximately corresponds to a Goldmann I_3e target, whereas the 200-asb stimulus is roughly equivalent to a Goldmann I_2e target (however, note that substantial individual differences appear to be present for the relationship between Goldmann and Fieldmaster response-equivalent stimuli). About 4.5 to seven minutes per eye were necessary to perform both tests on the Fieldmaster.

Previous investigations[1,2] have shown that to maintain a low false alarm rate, it is necessary to conduct an automatic recheck of all missed test spots, provide an optimal lens correction for testing the central 30 degrees at low stimulus luminances, and evaluate Fieldmaster test results according to well-defined, quantitative criteria for determining visual field defects. Reliable indicators of visual field defects on the Fieldmaster include: (1)

TABLE 2

OPTIMAL TEST CONDITIONS FOR THE FIELDMASTER MODEL 101-PR

Background luminance: 31.5
Stimulus duration: 0.8 sec
Interval between presentations: 0.9 sec
Stimulus color: White
Stimulus luminances: 635 asb (meter reading, 135) and 200 asb (meter reading, 44)

Test conditions:

Test 1: Full field examination, no lens correction, 635 asb (meter reading, 135) stimulus. For high refractive errors, do central 30 degree field examination with correction, and periphery only examination without correction at 635 asb (meter reading, 135) stimulus luminance; record results on same sheet of paper

Test 2: Using a separate sheet of paper, do central 30 degree field examination with proper refractive correction at stimulus luminance of 200 asb (meter reading, 44)

marked contraction of a substantial portion of the visual field, for example, a quandrantanopia; (2) two or more adjacent test spots missed on a single test run (one stimulus luminance), surrounded by locations that were detected; and (3) a single test spot missed on two or more successive test runs at different stimulus luminances, surrounded by locations that were detected. Nonindicators of visual field defects include: (1) a single test spot missed at only one stimulus luminance; and (2) test spots that were missed at high stimulus luminances, but were detected at lower stimulus luminances. The rationale for these criteria has been previously described.[1,2]

Our kinetic test procedure on the Goldmann perimeter consisted of at least two isopters beyond 30 degrees, three isopters within 30 degrees, and extensive spot-checking between isopters within the central 40 degrees (Fig. 3). This procedure has been previously described by Portney and Krohn,[10] and requires approximately 15 to 20 minutes for normal eyes, and up to 30 minutes or more for eyes with visual field defects.

Discrepancies between Fieldmaster results and kinetic visual field plots on the Goldmann perimeter were evaluated with thorough static perimetry on the Tübingen perimeter to provide a definitive answer. Additionally, nearly all of the 226 eyes of patients with ocular hypertension or glaucoma received extensive static perimetry in conjunction with manual kinetic testing and automated perimetry. Our standard procedure on the Tübingen perimeter consists of two kinetic isopters beyond 30 degrees to evaluate the peripheral visual field, static perime-

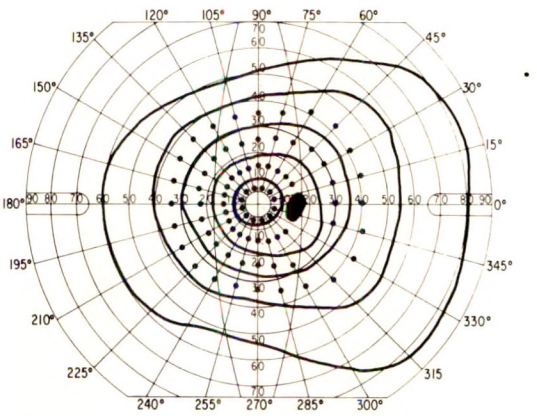


Fig. 3 (Johnson and Keltner). Manual kinetic test procedure used on the Goldmann perimeter for comparison with automated testing. Dark spots indicate the locations of "spot-checks" between isopters.

try along 11 meridians within the central 30 degrees to examine the central visual field thoroughly, plus any additional circular or radial static profiles necessary to define areas of known or potential visual field loss (Fig. 4). This procedure has been shown to be the most accurate and sensitive form of visual field testing that we have used,[1,2] and requires approximately 45 to 60 minutes per eye to complete.

Results

Detection and false alarm rates for the Fieldmaster automated visual field examination and manual kinetic testing on the Goldmann perimeter are presented in Table 1. For all patient categories, the Fieldmaster's detection rate was 90% or better, with a false alarm rate of less than 7%. Results for the total group of 1,019 eyes indicated that the Fieldmaster exhibited an overall detection rate of 96.1% and a false alarm rate of 4.7%. With the exception of one category (optic nerve disease other than glaucoma), manual kinetic testing on the Goldmann perimeter showed a higher detection rate and a lower false alarm rate than for automated Fieldmaster testing. However, none of these differences between automated and manual perimetry were statistically significant ($P>.05$, test of significance between two proportions).

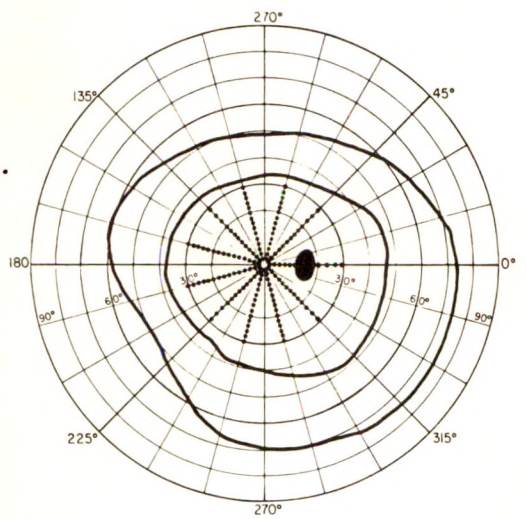


Fig. 4 (Johnson and Keltner). Manual static test procedure used on the Tübingen perimeter for comparison with automated Fieldmaster and manual kinetic testing.

In contrast, the patient category of optic nerve disease other than glaucoma showed a detection rate of 100% for the Fieldmaster as compared to only 86% for manual kinetic testing on the Goldmann perimeter. This difference in detection rate was statistically significant ($P<.0001$, test of significance between two proportions). Each of the 17 visual field defects in this category that were detected by the Fieldmaster and missed by manual kinetic perimetry, were confirmed by thorough static testing on the Tübingen perimeter. Because manual static testing with the Tübingen perimeter revealed the visual field defects, these differences found in optic nerve disease were probably the result of moving vs stationary targets rather than automated vs manual perimetry per se.

The detection and false alarm rates for the study of these 1,019 eyes are similar to the results obtained from our preliminary study of 135 eyes (detection rate = 98%; false alarm rate = 4.0%).[1] These findings indicate that the Fieldmaster is able to detect visual field defects as accurately as careful manual kinetic testing on the Goldmann perimeter. In most instances, correspondence between Fieldmaster results and Goldmann plots was good; only a small percentage of eyes showed poor correspondence between the two tests. Examples of good correspondence, poor correspondence, visual field defects missed by the Fieldmaster, visual field defects missed by manual kinetic perimetry, and characteristic Fieldmaster plots of visual field defects associated with various disorders have been reported previously.[1,2]

The value of the Fieldmaster automated perimeter in the follow up of patients with sequential visual field evaluations was also examined. One hundred sixty-eight (16.5%) of the 1,019 eyes in this study were tested with both manual kinetic perimetry and automated Fieldmaster testing on two or more visits during an 18-month period. The purpose of this evaluation was to determine the reliability and reproducibility of Fieldmaster test results, and to evaluate the Fieldmaster's capabilities for following the progression or regression of visual field defects. Because only 36 of the 168 eyes (21.4%) actually showed progression or regression of visual field loss, the findings for this portion of the study should be regarded as preliminary.

A summary of the results for this portion of the study is presented in Table 3. The Fieldmaster correctly identified 34 of the 36 eyes (94.4%) that showed progression or regression of visual field loss with manual kinetic testing on the Goldmann perimeter. Both of the eyes for which progression or regression of visual field loss was not apparent on Fieldmaster plots showed subtle, yet consistent visual field changes. The Fieldmaster also correctly identified no progression or regression of visual field loss in 131 of the 132 eyes (99.2%) that displayed no changes for manual kinetic testing on the Goldmann perimeter. Differences between manual kinetic testing (Goldmann perimeter) and automated perimetry (Fieldmaster) for determining progression or regression of visual field loss were not statistically significant ($P > .05$, test for significance between two proportions).

Our present data indicate that the Fieldmaster Model 101-PR shows a high degree of reproducibility and reliability for testing the visual field on successive visits, and is able effectively to determine progression or regression of visual field defects. However, two additional aspects of this analysis must be considered:

1. All of the 36 eyes that displayed progression or regression of visual field loss had retinal, optic nerve, or postchiasmal disorders. Therefore, we are not able to directly examine the Fieldmaster's ability to follow the progression of visual field loss in glaucoma until further studies are done. As a preliminary working hypothesis, we may infer that the ability to follow changes in visual field loss associated with glaucoma should be comparable to the results for other optic nerve disease.

2. Despite no statistically significant differences in determining progression or regression of visual field loss, it is clear that visual field plots generated by manual kinetic perimetry on the Goldmann are much easier to interpret than the output produced by automated Fieldmaster testing. Subtle changes in the visual field successive visits are difficult to evaluate with the Fieldmaster and are

TABLE 3

PROGRESSION OR REGRESSION OF VISUAL FIELD DEFECTS FOR AUTOMATED (FIELDMASTER) AND MANUAL KINETIC (GOLDMANN) PERIMETRY*

	No.	%
Progression or regression (manual)	36	100
Progression or regression (automated)	34	94.4
No progression or regression (manual)	132	100
No progression or regression (automated)	131	99.2

* Total number of eyes, 168.

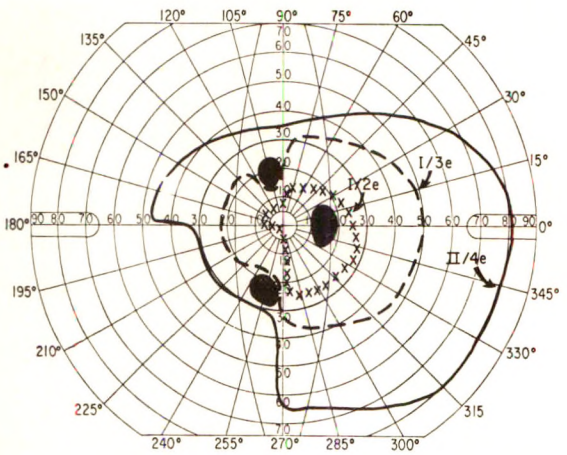
sometimes missed. Despite these criticisms, the Fieldmaster appears to perform surprisingly well for determining progression or regression of visual field defects.

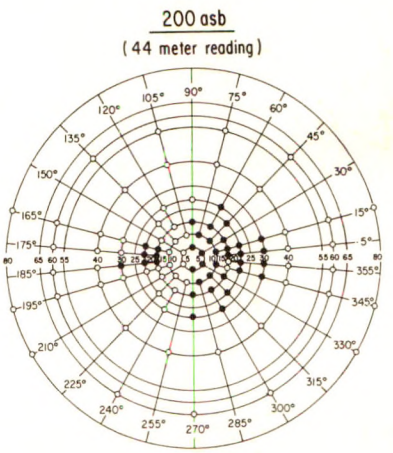
An example of progression of visual field loss, as determined by both automated (Fieldmaster) and manual kinetic (Goldmann) perimetry, has been presented in a previous paper for a case of retrobulbar neuritis associated with multiple sclerosis.[1] Additional examples of progression or regression of visual field loss revealed by manual and automated perimetry are presented here.

Case reports

Case 1—A 51-year-old man had gradual loss of vision in his left eye over a four-month period. Neuro-ophthalmologic examination revealed a visual acuity of 6/6 (20/20) in both eyes, normal color vision, no Marcus Gunn pupil, and normal fundi. Automated and manual visual field testing showed a highly incongruous left homonymous visual field defect. The patient had a craniopharyngioma involving the right optic nerve and right side of the chiasm and tract, confirmed by craniotomy. Approximately six months after surgery, a substantial portion of the visual field defect had resolved in both eyes.

Figure 5 shows kinetic visual field results on the Goldmann perimeter (Fig. 5, top left) and Fieldmaster plots for 200 asb (Fig. 5, top right) and 635 asb (Fig. 5 bottom right) for this patient's right eye before the craniotomy. Kinetic perimetry on the Goldmann revealed a wedge-type defect in the inferior





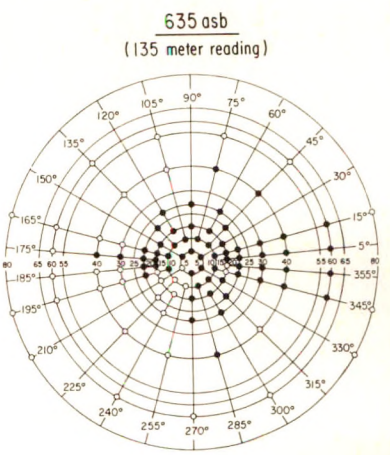


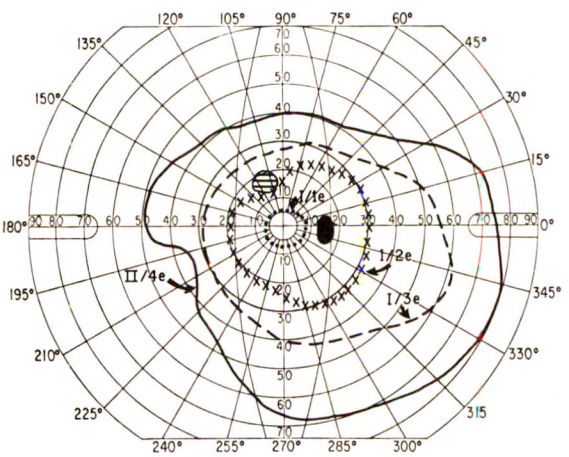
Fig. 5 (Johnson and Keltner). Manual kinetic visual field results (top left) and Fieldmaster plots at 200 asb (top right) and 635 asb (bottom right) for the right eye of a patient with a craniopharyngioma involving the right optic nerve and right side of the chiasm and tract. The scotomas shown in the kinetic plot (top left) were plotted with a II_4e target.

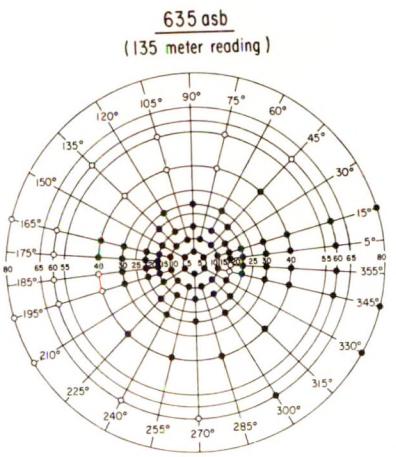
nasal quandrant, two moderately deep paracentral scotomas at 105 and 255 degree meridians, and the presence of a vertical step for the I_2e isopter. The central 30 degree Fieldmaster plot for the 200-asb (meter reading, 44) test accurately reflects the vertical step and the two paracentral scotomas, whereas the full field 635-asb (meter reading, 135) test reveals the inferior nasal wedge defect. Correspondence between manual kinetic testing and automated Fieldmaster results was good.

Approximately six months after the craniotomy, the patient's visual field evaluations for the right eye were done (Fig. 6). The Goldmann visual field plot (Fig. 6, top left) indicates a significant improvement in the patient's visual field, with only a shallow paracentral scotoma at 105 degrees and a slight remnant of the inferior nasal wedge defect remaining as areas of sensitivity loss. The 200-asb (meter reading, 44) Fieldmaster plot for the central 30 degrees shows a suggestion of the paracentral scotoma at 105 degrees and the inferior nasal wedge, and the 635-asb (meter reading, 135) full field test is essentially normal except for the indication of a slight inferior nasal wedge defect. Both Fieldmaster and Goldmann visual field plots thus show a distinct improvement in visual field sensitivity between the first and second examinations. Similar visual field improvements were also present in the left eye.

Case 2—A 22-year-old woman had grayouts of vision, beginning in February 1977. The grayouts were particularly associated with postural changes, would occur approximately three to four times per hour, and last for about 15 seconds. Neuro-ophthalmologic examination revealed a visual acuity of 6/6 (20/20) in both eyes, 8 to 10 prism diopters of esotropia, and 4+ papilledema in both eyes. Visual field testing showed greatly enlarged blind spots in both eyes. Neurologic and ophthalmologic examinations were consistent with a diagnosis of pseudotumor cerebri. The patient was treated with 250 mg of acetazolamide (Diamox) four times per day. During the subsequent 16 weeks, the patient's visual obscurations and grayouts ceased, a large amount of her papilledema resolved, and the size of her blind spots on visual field testing were reduced.

Results of kinetic testing on the Goldmann perimeter and automated Fieldmaster perimetry for this patient's right eye are presented in Figure 7. Before





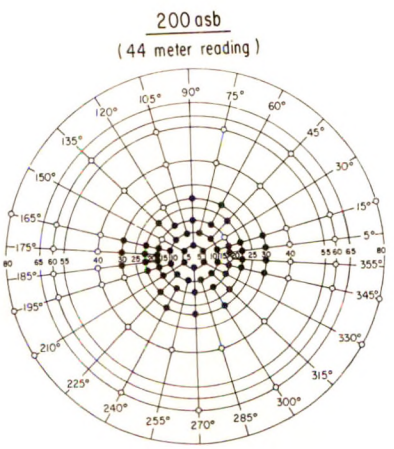


Fig. 6 (Johnson and Keltner). Manual kinetic visual field results (top left) and Fieldmaster plots at 200 asb (top right) and 635 asb (bottom right) for the eye shown in Figure 5, six months after the patient underwent surgery. The scotoma (cross-hatching) on the kinetic examination was plotted with a I_3e target.

treatment, the kinetic visual field plot on the Goldmann (Fig. 7, top left) revealed a greatly enlarged blind spot, forming a shallow to moderately deep scotoma in the centrocecal region. The 200-asb (meter reading, 44) Fieldmaster plot for the central 30 degrees also shows an enlarged blind spot (Fig. 7, top right), although the extent of the deficit is not as large as that found by kinetic testing on the Goldmann perimeter. An enlarged blind spot was also evident on the full field 635-asb (meter reading, 135) Fieldmaster plot (not shown). After treatment (approximately 16 weeks later), the kinetic visual field plot showed a resolution of most of the visual field defect (Fig. 7, bottom left), which was also present on the 200-asb (meter reading, 44) Fieldmaster plot (Fig. 7, bottom right). Similar results were obtained for the patient's left eye.

The case reports outlined above show that the Fieldmaster Model 101-PR is able to show progression or regression of visual field defects to a certain degree. However, they also show that manually-derived kinetic plots may be more readily interpreted than the automated Fieldmaster results for determining visual field changes.

Discussion

A number of studies[1–10] have now shown that automated static or supra-

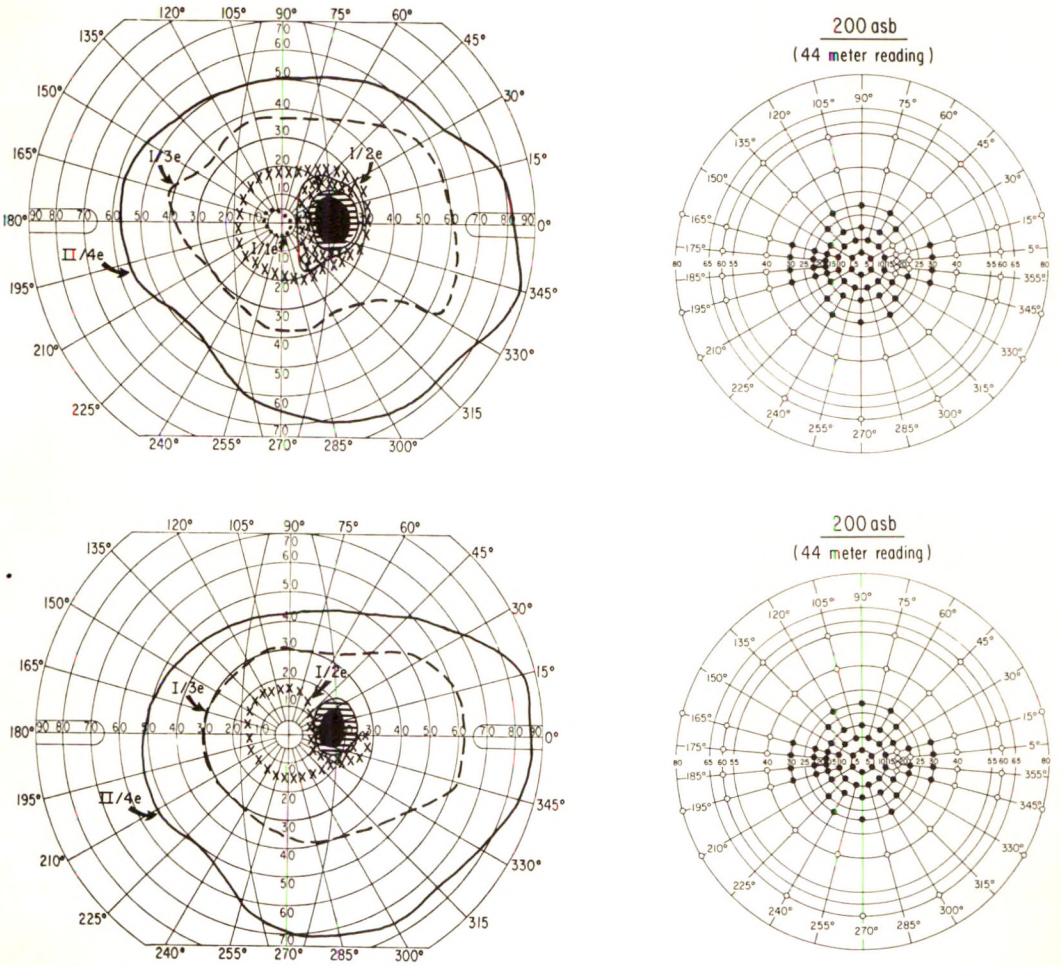


Fig. 7 (Johnson and Keltner). Manual kinetic visual field results (left) and Fieldmaster plots at 200 asb (right) for the right eye of a patient with papilledema secondary to pseudotumor cerebri. The top graphs present the findings on the initial visit and the bottom graphs show the visual field results after 16 weeks of treatment. For kinetic testing, blind spots were plotted with the II_4e (filled area), I_3e (crosshatched area), and I_2e (enclosed x's) targets.

threshold static perimetry is capable of detecting visual field defects as accurately as manual kinetic testing conducted by highly skilled technicians. Our present evaluation of more than 1,000 eyes also indicates that automated suprathreshold static perimetry shows an overall detection rate that is comparable to manual kinetic testing, and actually performs statistically significantly better for patients with optic nerve disease other than glaucoma. These differences in optic nerve disease probably reflect the use of moving vs stationary targets rather than differences between manual and automated perimetry per se. The high detection rate and low false alarm rate of the Fieldmaster Model 101-PR indicate that it is an excellent quantitative screening device for detecting visual field defects.

Preliminary results obtained for 168 eyes suggest that the Fieldmaster Model 101-PR may be capable of following the progression or regression of visual field defects. More than 94% (34 of 36) of the eyes that showed progression or regression of visual field loss with manual kinetic perimetry were correctly identified by automated Fieldmaster testing. Additionally, the Fieldmaster correctly showed no change in more than 99% (131 of 132) of the eyes that displayed no progression or regression of visual field defects on manual kinetic testing with the Goldmann perimeter. Although these results are good, two additional factors must also be considered:

1. It is more difficult to assess progression of visual field loss with Fieldmaster plots than with visual field charts derived from manual kinetic testing with the Goldmann perimeter. Subtle changes in visual field characteristics may not be accurately defined by the Fieldmaster.

2. Eyes with progression of glaucomatous visual field defects have not yet been evaluated with the Fieldmaster. Data for glaucoma patients with progressive visual field loss may be difficult to obtain because of the slow progression of the disease process, particularly in patients receiving appropriate treatment and follow-up examinations. Assuming that it is reasonably valid to extrapolate from other optic nerve diseases, we anticipate that the Fieldmaster may be able to provide a satisfactory means of monitoring glaucomatous visual field loss in many instances. Further evaluations of progression or regression of visual field loss with the Fieldmaster will be necessary to determine its capabilities and limitations in this regard.

The Fieldmaster Model 101-PR is an excellent quantitative screening device for detecting visual field defects, and also appears to have some capabilities for determining progression or regression of visual field loss. Other advantages of this type of automated perimetry include standardization of test conditions and procedures, greater time and cost effectiveness, electronic monitoring of eye position and the ability of personnel with little or no training in perimetry to conduct the testing. Another important consideration for both automated and manual perimeters is the dependability of the instrument. We have been favorably impressed with the Fieldmaster in this regard. In the two years that we have extensively used the Fieldmaster, only one or two minor problems were encountered. We have now performed Fieldmaster visual field testing on over 2,000 eyes.

The major disadvantages of this type of automated perimetry presently include data representation and limited flexibility. The Fieldmaster and related devices use a method of presenting visual field results that is generally more difficult to interpret than standard kinetic plots derived from the Goldmann perimeter. An improvement in the representation of data from automated suprathreshold static perimetric testing would greatly facilitate the use of this test procedure. Also, the

use of fixed, predetermined test locations places certain constraints on the capabilities and flexibility of the test procedure. Despite these two factors, the Fieldmaster Model 101-PR performed well.

Automated suprathreshold static perimetry, such as performed by the Fieldmaster Model 101-PR, should be regarded as a supplement to existing methods of visual field testing, rather than as a replacement for manual perimetric methods. However, with the use of proper test conditions, we believe the Fieldmaster can be a valuable addition to visual field testing. A busy ophthalmologist's office may not be conducive to performing careful, quantitative (and time-consuming) kinetic perimetry. Under these circumstances, automated devices such as the Fieldmaster may provide a viable alternative to kinetic perimetry. Automated testing could also be supplemented by the ophthalmologist's previous visual field testing methods for cases in which more extensive information is required. This type of approach may allow more patients to receive reliable, quantitative visual field testing. From a pragmatic standpoint, automated perimetry is now a reality that offers a number of distinct advantages for the practicing ophthalmologist, assuming that proper test procedures are used.

Summary

Automated (Fieldmaster) and manual kinetic perimetry were performed in 1,019 eyes with various visual disorders. Under appropriate test conditions, automated Fieldmaster evaluations showed a 96.1% detection rate and a 4.7% false alarm rate for detection of visual field defects. Preliminary results for 168 eyes showed that sequential follow-up testing with the Fieldmaster correctly identified progression or regression of visual field loss in more than 94% (34 of 36) of the eyes with visual field changes. The Fieldmaster correctly determined no change in visual field characteristics for 99% (131 of 132) of the eyes with stable visual fields. These data indicate that the Fieldmaster is an excellent device for detecting visual field defects, and also has some capabilities for monitoring progression or regression of visual field loss.

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NOTES, CASES AND INSTRUMENTS

A MODIFIED ARTIFICIAL ANTERIOR CHAMBER FOR USE IN REFRACTIVE KERATOPLASTY

EZRA MAGUEN, M.D., RICHARD A. VILLASEÑOR, M.D., DONALD E. WARD, B.A., AND ANTHONY B. NESBURN, M.D.

Los Angeles, California

The artificial anterior chamber[1] was originally developed to allow anterior trephination of corneas preserved in McCarey-Kaufman medium. We modified the instrument so that it could be used to produce lamellar corneal sections with the Barraquer microkeratome.

The microkeratome[2] is capable of performing high quality lamellar corneal sections. The instrument is used mainly in refractive keratoplasty, but can be an effective tool in performing lamellar corneal transplants. With the Barraquer system, microkeratome keratectomies can be done only in vivo, or on whole donor eyes. The widespread use of McCarey-Kaufman medium for corneal preservation[3] provided impetus to design an instrument that could allow making lamellar corneal sections with the microkeratome on these readily available donor corneas.

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MATERIAL AND METHODS

The instrument (Fig. 1) is made of Teflon and stainless steel.* The main working components are a black Teflon dome, which incorporates a hydraulic system consisting of a modified Yale BD needle hub and a bored passageway within the dome. A fixation ring fits into the angular landing near the top of the dome. A pair of stainless steel springs holds the ring in place and supplies even tension around its circumference. When the donor cornea is in position, an even pressure is applied to the scleral rim by the securing ring. This creates a seal by forcing the sclera into close contact with the Teflon dome. A positive pressure within the artificial anterior chamber is formed by using McCarey-Kaufman me-

*The artificial anterior chamber is available from Ophthalmic Specialties, P.O. Box 27, San Gabriel, CA 91778.

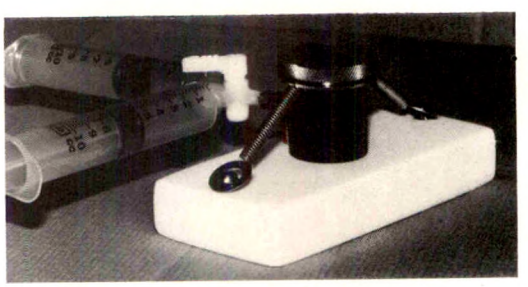

Fig. 1 (Maguen and associates). A human cornea is mounted on the modified artificial anterior chamber by using the adjustable two piece fixation rotating ring device. Positive pressure of 60 mm Hg is created by injecting known amounts of air and McCarey-Kaufman medium. The rotating ring containing the microkeratome tracks is threaded in place.

dium injected through the syringe fitting.

The modifications of the system for use with the Barraquer microkeratome include the following: (1) use of a combination of McCarey-Kaufman medium and air within the hydraulic system to produce a high pressure compressible system, which provides reliable pressures of 60 mm Hg or more necessary to obtain reproducible lamellar sections; (2) fabrication of an adjustable fixation rotating ring assembly to accomodate the microkeratome, so various size lamellar donor sections could be cut. The device is a precisely machined two-piece assembly. The upper portion or rotating ring threads onto the lower portion or fixation ring, which seals the donor cornea in position.

The rotating ring contains tracks to accommodate the microkeratome similar to those found on the Barraquer suction rings. The height of this rotating ring can be varied by rotating it on the fixation ring threads. This exposes varying amounts of corneal tissue to the microkeratome blade, thereby modifying the diameter of the lamellar section. The system allows the use of the presurgical tonometer and the set of special applanation lenses that are part of the Barraquer microkeratome system.

To use the instrument, the surgeon fills one syringe with air and a second with McCarey-Kaufman medium. Disposable 5-ml syringes are used. The syringes are connected to the needle hub at the base of the Teflon dome via the two-way stopcock. The central passageway is filled with McCarey-Kaufman medium until a fluid meniscus forms on the dome's flattened top. The cornea is then carefully placed on top of the dome without disrupting the fluid meniscus. The fixation ring is then placed over the cornea and its springs secured to the base of the instrument. The chamber is filled with McCarey-Kaufman medium and is brought up to a pressure of 60 mm Hg as measured by the presurgical tonometer. McCarey-Kaufman medium (0.2 ml) is withdrawn and is replaced with air until the pressure in the anterior chamber is brought to 60 mm Hg again.

Finally, the rotating ring is threaded onto the fixation ring. The diameter of the lamellar section is measured with the Barraquer applanation lens. The rotating ring is turned until the diameter of the applanated cornea matches the ring engraved in the applanation lens. The thickness of the lamellar section is determined by inserting the appropriate stainless steel plate in the head of the microkeratome. The intraocular pressure is checked again and more air is introduced if necessary, to bring the pressure to 60 mm Hg. The microkeratome head is slid onto the track of the rotating ring and the lamellar section is done (Fig. 2).

Summary

We devised a modified artificial anterior chamber that enables Barraquer microkeratome keratectomies on corneas

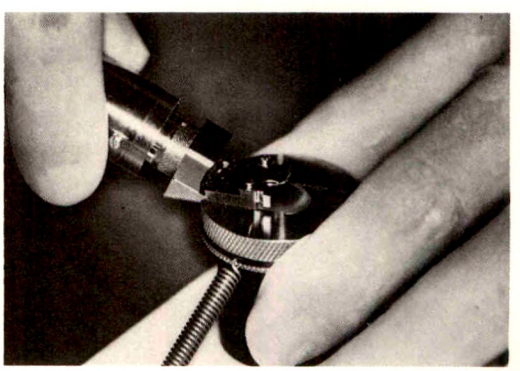

Fig. 2 (Maguen and associates). The microkeratome head is inserted onto the tracks of the rotating ring and the microkeratome section is done.

preserved in McCarey-Kaufman medium. It consists of a hydraulic system, which creates a positive pressure of 60 mm Hg or more. An added rotating ring serves as a base to the microkeratome's tracks and varying diameters of lamellar sections can be obtained. This device allows the surgeon to use readily available corneas with scleral rims preserved in McCarey-Kaufman medium rather than whole eyes to obtain precise lamellar sections.

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NEW FORCEPS AND CUTTING BLOCK FOR DONOR CORNEAS

Frederick S. Brightbill, M.D., and Brad Calkins, B.S.

Madison, Wisconsin

We designed 0.12-mm media forceps* for removal of the corneoscleral rim when stored in short-term solutions such as McCarey-Kaufman medium. A 7.0-cm length shaft is sufficiently long to minimize the possibility for contamination of the surgeon's gloves while the cornea is removed from a 20-ml solution bottle (Fig. 1, left). The cross-action design combined with 0.12 mm double-pronged, opposing teeth allows positive closure over the scleral edge and sure first-attempt retrieval of the donor tissue (Fig. 1, right).

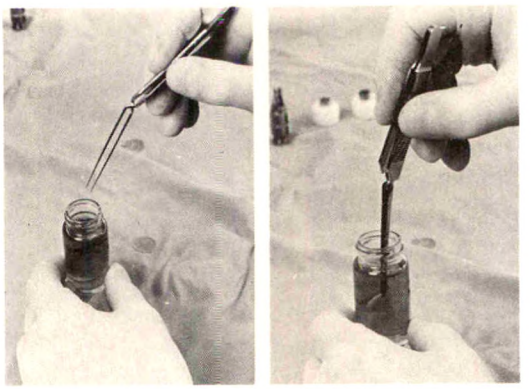

Fig. 1 (Brightbill and Calkins) Left, Cross-action angled media forceps with 20-ml media storage bottle. Right, Media forceps engaging edge of corneoscleral tissue stored in media.

Variable-curved wells are a new con-

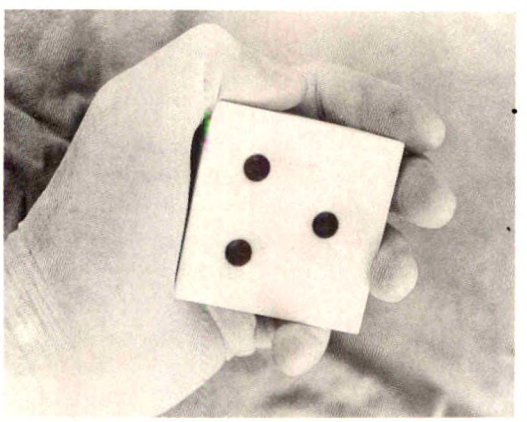

Fig. 2 (Brightbill and Calkins). Variable-curved wells (15 mm, 16.5 mm, and 18 mm) with centering targets in a Teflon block.

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*Both instruments are available from Storz Instrument Co., St. Louis, Missouri.

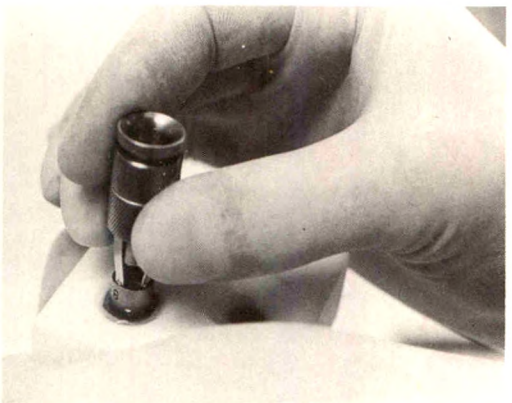

Fig. 3 (Brightbill and Calkins). The surgeon uses the corneal trephine to punch the corneoscleral tissue by using the endothelial-side maneuver with the Teflon cutting block.

cept in the design of a block for use with handheld trephines using the endothelial punch technique[1-2] for cutting donor buttons.* The block (Fig. 2) incorporates three wells per side (total of six) with three different base curves manufactured by using one half circle end mills of 15 mm, 18 mm, and 20 mm (we have omitted the 20-mm well [flattest] in newer blocks while inserting a 16.5-mm diameter well for improved corneoscleral rim fitting). This allows the surgeon to choose the well that is the best fit before punching out the donor button (Fig. 3). Eight-millimeter red centering targets assure improved centering of the punching trephine. Made from Teflon, the block's dimensions (58 × 58 × 20 mm) were designed for easy use either in the palm of the surgeon's hand or on the instrument table top.

Whenever a punching maneuver is used over a Teflon surface, the edges of the donor button must be carefully inspected for adherence of small fragments of Teflon. We have observed that the punched button will always remain in the well when used in conjunction with any new 0.25-mm stepped disposable trephine blade.

Summary

We designed two new instruments to faciliate the handling and cutting of donor corneal buttons: 12-mm media forceps and a varible curved Teflon block with centering targets.

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ENHANCEMENT OF RETINAL FLUORESCEIN BIOMICROSCOPY

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Visualization of fluorescein through a slit lamp and contact lens can be enhanced through proper selection of exciting and barrier filters.[1-3] We devised an optical bench model of the American Optical 11666 slit lamp to test filter combinations of theoretical value. We compared clinically selected filter combinations to determine effectiveness when mounted in a slit lamp.

Material and Methods

An optical bench model of the American Optical 11666 slit lamp was con-

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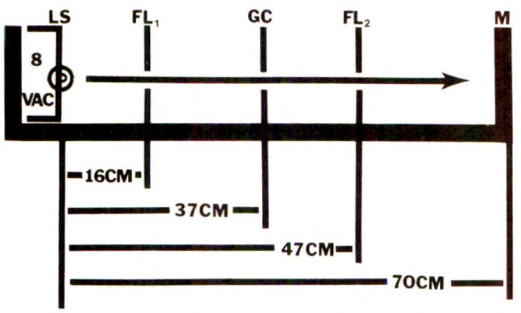

Fig. 1 (Chambers). Slit-lamp bench model. Light (arrow) from an 8-V light source (LS), passes through exciter filter (FL_1), fluorescein chamber (GC), barrier filter (FL_2), and is recorded with light meter (M).

TABLE

TRANSMISSION OF LIGHT THROUGH EXCITER AND BARRIER FILTERS

Filter		
Exciter	Barrier	Foot Candles
5850	None	19
5850	58	15
5850	SB-50	5
47	None	24
47	58	20
SE-40	None	0.85
SE-40	SB-50	0.31
None	None	500

structed of wood coated internally with low reflectant black pigment (Fig. 1). Exciting and barrier filters were placed at distances to correspond with their position when permanently mounted in the slit lamp. The fluorescein chamber and light meter were positioned to correspond to patient and observer retinas respectively. A single GE-1468 lamp powered by an 8-V AC parallel electrical circuit from a slit-lamp terminal served as the light source. Exciting filters were placed at 16 cm from the light source. A glass-walled chamber was placed at 37 cm and filled with a 250-μ thick solution of 10% fluorescein. Barrier filters were placed at 46 cm from the light source. A Gossen lunasix 3 light meter was used to record light at 70 cm from the light source. Exciting filters were tested alone and in combination with barrier filters. Corning 5850, Kodak Wratten No. 47, and Spectrotech SE-40 exciting filters and Kodak Wratten No. 58 and Spectrotech SB-50 barrier filters were evaluated. For clinical evaluation, the exciting filters were placed in the filter disk and barrier filters mounted in front of the objective lens of the slit lamp. Fluorescein (10%) was injected intravenously and observed in the retinal vessels through a coated Goldmann contact lens. An assistant rotated various filters into place during observation of each patient.

RESULTS

The amount of light recorded in foot candles for each exciting filter alone and combined with a commonly used barrier filter is shown in the Table. The amount of measured light is inversely proportional to the effectiveness of the filter combination. Clearly, the combination of the SE-40 exciting filter and SB-50 barrier filter is the most effective of those tested for use in a slit lamp (Fig. 2).

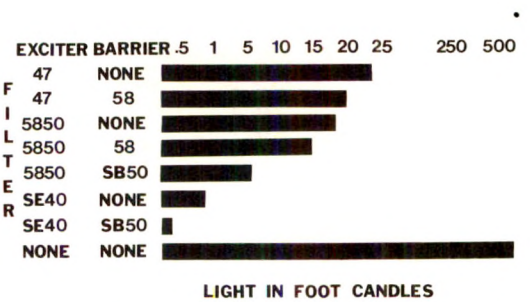

Fig. 2 (Chambers). Transmission of light through exciter and barrier filters. The amount of light recorded is inversely proportional to filter effectiveness.

Three observers independently rated the effectiveness of the SE-40 and SB-50 filter combination to be superior. The argon laser aiming beam was easily seen through the barrier filters.

Discussion

Visualization of fluorescein through a slit lamp is enhanced by selection of exciting and barrier filters. Incorporation of filters into the slit lamp allows easy localization and observation of subretinal new vessels,[4] leaking sites in central serous choroidopathy,[5] and vascular changes in diabetic retinopathy[6] during photocoagulation.

The aiming beam of the argon laser remains visible through the SB-50 filter and direct photocoagulation of leaking sites is much easier than photocoagulation from enlarged angiograms. External fluorescein applied to the cornea is better visualized with a barrier filter than without.

The exciting filter proved to be more important than expected in visualizing fluorescein. Use of the SE-40 filter alone without a barrier filter allows visualization of retinal vessels just as well as the less effective exciter barrier combinations. The SE-40 and SB-50 combination gave such clarity of the observed retinal vessels that they were preferred by each observer.

Summary

We constructed an optical bench model of the American Optical slit lamp to test effectiveness of several filters to enhance visualization of fluorescein. The filters varied considerably in light transmission. This variability of light transmission correlated well with the application of the filters in clinical practice.

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VIEWING FLUORESCEIN FILMS WHILE PERFORMING LASER TREATMENT

Marvin F. Kraushar, M.D.

New York, New York

While performing laser retinal photocoagulation for macular disease it is helpful to refer to a selected frame from the fluorescein study as a guide for accurate placement of the laser treatment. This is often accomplished by projecting a 35-mm slide on a screen. A large room is necessary to allow adequate magnification of the image, which is usually projected at a significant distance from the operator.

I devised an alternate method using a commercial desk top viewer (Fig. 1). The entire film strip (negative) or contact

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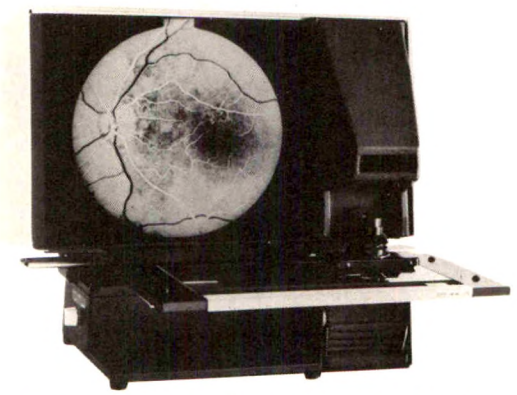

Figure (Kraushar). Desk top viewer showing a frame (positive) from the fluorescein study.

sheet (if transparent) can be placed on the tray and the operator can scan and select any desired frame or frames for viewing. The apparatus can be located on top of the laser with the viewing screen within arm's length. Most viewers produce a bright image approximately 9 inches in diameter with excellent resolution. This avoids both the need for a large room and the necessity of mounting film in frames for use in a slide projector.

SUMMARY

I devised a method for viewing the fluorescein study while performing laser treatment for macular disease that uses a commercial desk-top viewer located on the top of the laser.

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CHROMOSOMES, EMBRYONAL TUMORS, AND BIRTH DEFECTS

High resolution chromosome analysis has dramatically changed the impact of cytogenetics on each of the clinical disciplines, and nowhere is this more true than for ophthalmology, especially when the focus is on congenital anomalies and embryonal tumors. Gram for gram the eye probably has more specified functions and components than any other body part. Thus, a subtle or singular defect may be recognized which requires sophisticated technology for demonstration of an otherwise inapparent cause. My own experience has been convincing that anatomic defects of the eye in an infant, when no other anomalies of functional defects may be apparent, can be a potent indicator of a chromosome aberration. In this context the purposes of this editorial are to encourage even closer, earlier collaborations between ophthalmologists and cytogeneticists and to comment on possible pathogenetic relationships between two specific chromosome aberrations and the embryonal tumors that apparently result from them. The immediate consequence of the collaboration is improved care for the patient and his family; the long-range consequences are the potential for unique insights into karyotype-phenotype correlations in general and the pathogenesis of embryonal tumors in particular.

Retinoblastoma caused by deletion of chromosome 13,[1] and the aniridia-Wilms tumor association caused by deletion of chromosome 11's short arm,[2,3] have provided uniquely compelling circumstances for exploring the causal relationships between the genetic changes and resultant aberrations in tissue organization and cell growth. Cytogenetics has effectively passed the "show and tell" stage of its development when we merely juxtaposed clinical findings on the one hand and rather crude cytogenetic findings on the other, with conclusions about causal relationships and mechanisms left to extraordinary imaginations. Using high-resolution banding analysis of prophase chromosomes it is now possible to recognize the presence, loss, or gain of 1,200 or more very small segments of the chromosome complement.[4] Moreover, the tech-

nology required for maximum chromosome resolution is straightforward and readily accessible. These factors underlie the progressive merging of interests common to ophthalmology, birth defects, oncology, and cytogenetics. Closer, more widespread collaborations will lead to more precise investigations into pathogenetic sequences and enhanced health care in terms of individualized therapies, accurate prognostications, and accurate genetic counseling.

The key to further progress, however, is the timely availability of blood and tumor samples from all patients with retinoblastomas, Wilms tumors, and aniridia. From a clinical vantage point, the demonstration of a constitutional defect in blood lymphocytes would then require chromosomal evaluation of family members and determine prognosis in terms of associated anomalies. A chromosome aberration in the tumor alone would strongly argue against a Mendelian mutation as the tumor's cause. The absence of a chromosome aberration in lymphocytes or tumor would suggest such a mutation as a possible primary cause.

On a more basic investigative level, the article by Nichols and associates in this issue of THE JOURNAL emphasizes the types of cytogenetic approaches that can be applied for sorting out specific genetic alterations that could account for retinoblastoma, the aniridia-Wilms tumor association and similar problems. Two types of chromosomal aberrations have been associated with retinoblastoma: sex chromosome aneuploidy (XXX or XXY), with and without trisomy 21, and, more commonly, deletion of chromosome 13's long arm, characteristically involving the q14 band [del(13q14)].[2] In all previous cases involving chromosome 13, the critical segment (13q14) appears to have been literally lost from the genome, and physical stigmata other than retinoblastoma are readily apparent, although sometimes subtly.[5] Nichols and associates suggest that functional, not literal, deletion of 13q14 accounts for their patient's retinoblastoma: By virtue of "spreading" of the heterochromatinization from Xp to the translocated, contiguous 13q functional loss of 13q14's genetic activity is proposed. My major concern with this hypothesis is lack of an unequivocal change in the R-banding of the translocated 13q segment to the heterochromatic pattern when its attached X-chromatin has the late-labeling pattern. An alternative explanation, secondary interstitial deletion of 13q14 in the translocated segment, has been suggested[6] and discounted. Another possibility is change in either chromosome 13's q14 band in the tumor itself and nowhere else.

Another embryonal tumor, nephroblastoma or Wilms tumor, has also been associated with a chromosomal deletion, this time of chromosome 11's short arm band 13 [that is, del(11p13)].[2,3] Moreover, del(11p13) with Wilms tumor is always associated with aniridia, although it is not true that all instances of the aniridia-Wilms tumor have del(11p).[7] Additionally several instances of aniridia with del(11p13) are known without Wilms tumor, including one of a pair of monozygous twins whose co-twin has the tumor.[8]

The progressively smaller sizes of microscopically apparent del(13q14)[5] and del(11p13),[8] plus the functional loss of genetic activity purported by Nichols and associates and our knowledge of the aniridia-Wilms tumor association without an apparent del(11p13) add up to suggest the use of closely linked genes to indicate loss of the critical chromosomal segment. For example, the esterase-D locus, assigned to 13q14, may be used to corroborate or even primarily indicate loss of that band or a portion thereof.[9] To this end Nichols and associates might have used decreases in esterase-D activity in native or cloned populations of their patient's cells to substantiate functional

loss of genetic activity of, or within, 13q14. The prospect of using a similar type of marker for del(11p13) would be especially useful in aniridia patients at risk for evolving into patients with aniridia-Wilms tumor association. Of the potentially useful 11p markers none will suffice, however; lactic dehydrogenase-A and acid phosphatase-2 are too distant on 11p12 and the 11p-assigned non-alpha globin loci, characterized by DNA restriction enzyme techniques, were intact in a boy whose del(11p) was essentially limited to 11p13.[7,8]

The case of Nichols and associates notwithstanding, most of the deletions of 13q14 associated with retinoblastoma and virtually all of the deletions of 11p13 associated with aniridia or the aniridia-Wilms tumor association have been interstitial, as opposed to being part of a reciprocal exchange.[8,10] This could mean, among other things, that interstitial deletions have special significance for embryonal tumor causation or that they merely entail small segments allowing survival into childhood with sufficient time for the tumor to become manifest, whereas large deletions would be fatal (for example, in utero) before the tumor becomes obvious. In any event, high resolution prophase analysis by experienced personnel must be used in the cytogenetic evaluation of these patients. I wish to re-emphasize the notion of the haplicon, a chromosomal segment, which when present singly leads to specified problems.[1] There is the aniridia-Wilms tumor association haplicon within 11p13 and the retinoblastoma haplicon within 13q14. Although it is tempting, we cannot yet conclude that there is a retinoblastoma gene per se in 13q14. On the one hand, what we can say is that 13q14's hemizygous presence characteristically leads to retinoblastoma. Whether the tumor results from a classical Mendelian gene mutation or another level of disruption of chromosomal function remains to be shown. On the other hand, either mechanism may not literally cause the tumor, but merely alters differentiation so that the target tissue is highly predisposed, much like the Y-chromosome in 45,X/46,XY or 46,XY gonadal dysgenesis predisposes to gonadal tumors. The Y-chromosome does not cause the tumor per se, it merely sets the stage by determining tissue differentiation. The presence of diffuse, but relatively specific, ultrastructural aberrations in the non-tumorous portion of the retina of del(13q) patients with retinoblastoma is consistent with this tissue differentiation hypothesis.[11]

Vincent M. Riccardi

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CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Orange Tears

Editor:

There have been numerous reports sent to the National Registry of Drug Induced Ocular Side Effects and one report in the nonophthalmic literature[1] of colored tears secondary to the systemic use of rifampin, a new semi-synthetic antibiotic. The tears are usually orange in color but may be light pink or even red. There have also been reports of staining of contact lenses and the inability to wear lenses while taking this drug. It has been suggested that patients may need to discontinue contact lens wear while taking rifampin.[1]

Apparently not all patients secrete this drug or a byproduct in their tears, but many do. Other ocular side effects occur in from 5 to 14% of the patients depending on the frequency and dosage of this agent. These vary from hyperemia, a mild blepharoconjunctivitis, to a painful, severe exudative conjunctivitis. The latter includes tender, markedly congested, palpebral and bulbar conjunctiva with thick, white secretions.[2] In general, the ocular side effects have been reversible when the drug has been discontinued.

Patients taking this medication usually have tuberculosis or are possible carriers of *Neisseria* meningitis. The drug is used in England as a 1% topical ocular ointment for ocular chlamydia infections.[3]

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Executive Director
National Registry of Drug Induced Ocular Side Effects
Portland, Oregon

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BOOK REVIEWS

The Proceedings of the XXIII International Congress of Ophthalmology. Edited by Koichi Shimizu and Jendo A. Oostehuis. Amsterdam, Excerpta Medica, 1979. Hardcover, 1,970 pages, table of contents, subject index, author index, 649 black and white figures, 21 color figures. $214.75

The Proceedings of the XXIII International Congress of Ophthalmology, held in Kyoto May 14-20, 1978, were distributed to participants in September 1979. Additional volumes for libraries, subscribers, and review were distributed in late 1979. These books provide the same insight into the meetings as have the Proceedings since the first International Congress in Brussels in 1857. The Kyoto meeting and these proceedings with the editing by Koichi Shimizu of Japan and Jendo A. Oosterhuis of The Netherlands can only be described in superlatives. Five hundred fifty-nine papers were presented. All except the lectures on recent advances in ophthalmology are included and these will be published separately.

The two main themes, "Immunology and immunopathology of the eye," and "Retinal pigment epithelium," are well done. The round table discussions on ocular toxocology, choroidal circulation, corneal diseases, optic neuropathies, pathology of the visual cells, vitreous surgery, and infection of the eye are timely and interesting. The symposia provided

by the International Organization against Glaucoma, the International Agency for the Prevention of Blindness, the International Study Committee for Teaching and Postgraduate Education, and the reports of the Satellite Symposia are also included. The remaining 24 chapters, mainly in English with a scattering of French, deal with nearly every aspect of ophthalmology.

The volumes are extremely attractive and well prepared, in keeping with the general excellence of organization of the entire XXIII International Congress. As with previous volumes, they will become collectors' items.

FRANK W. NEWELL

Ophthalmological Considerations in the Rehabilitation of the Blind. By Charles W. Hoehne, John G. Cull, and Richard E. Hardy. Springfield, Charles C Thomas, 1980. Hardcover, 313 pages, table of contents, preface, name index, subject index. $24.75

This book is an outgrowth of a conference held in 1974 in Houston, Texas. It is a compendium with contributions by 28 experts in blind rehabilitation or ophthalmology. Each chapter has been designed to give the reader as much information as possible in a brief format. The text contains information which should be more helpful to the ophthalmologist than to the rehabilitation worker; however, both can make use of this information in designing programs and establishing policies and philosophies. One would almost have to review each chapter individually in order to do justice to such a book, because each chapter is diverse though occasionally repetitive.

Of the several excellent chapters, I particularly recommend Chapter 4 by Cross on recent advances in genetics. Chapter 15 by Rives is a succinct and realistic evaluation of what blind people need, who the professionals are that can provide these needs, and how they should be provided.

Chapter 18 by Bledsoe can help the ophthalmologist become more knowledgable in regard to the special courtesies that make blindness easier. Chapter 26 by Hart introduces a program sponsored by the Research Foundation of Missouri, Inc. It is unfortunate the chapter does not have an update on its progress after six years.

There are interesting statistics by several authors. The statistics about blindness, and those who are considered to fall within the definition of blindness, are tenuous and hard to substantiate. However, these statistics do provide some guidelines. The figures suggest that the number of people who have severe visual impairment is probably much greater than usually assumed. There have been remarkable advances in certain areas since the inception of this book, hence many of the chapters are not completely current. This does not lessen their usefulness, however, because in most instances they allude to the possibility of these advances.

Certainly for information concerning the past, present, and a glimpse into the future of ophthalmology's role in the rehabilitation of those with loss of vision, this book is an excellent guide.

RICHARD E. HOOVER

Optic Neuritis and its Differential Diagnosis. By G. D. Perkin and F. Clifford Rose. New York, Oxford University Press, 1979. Hardcover, 292 pages, preface, table of contents, index, 92 black and white figures. $60.

This monograph is based on a series of 172 patients examined at the Royal Eye Hospital, London, during the period 1963 to 1969. The follow-up of any individual patient does not appear to have exceeded six years.

The book opens with an introduction containing anatomic, physiologic, and pathophysiologic information. The first chapter is a brief historical survey, followed by three chapters on methodology and epidemiology, symptoms and visual signs, respectively. Four chapters deal with differential diagnosis. Succeeding chapters cover cerebrospinal fluid in multiple sclerosis treatment, Uhthoff's syndrome, subsequent visual signs, prognosis for development of multiple sclerosis, methods for detecting optic nerve demyelinization, and the relationship of optic neuritis to multiple sclerosis.

In the discussion on the relationship between optic neuritis and multiple sclerosis in Chapter 13, the authors attempt to delineate the criteria for identifying a demyelinizing process affecting the nerve. They properly point out that in many cases the diagnosis of optic neuritis is one of exclusion. They tend toward the definition of Nettleship that optic neuritis is "a failure of sight limited to one eye, often accompanied by neuralgic pain about the temple and orbit and by pain on moving the eye." They express doubt that bilateral involvement within a short span of time should be included, or that retrobulbar neuritis, without edema of the optic disk should be equated with optic neuritis.

The terms, "atrophy and pallor," as applied to the appearance of the optic disks, are used interchangeably throughout the book. However, considerable degrees of pallor may remain after an attack of neuritis even with no demonstrable residual optic atrophy as determined by sophisticated analysis of visual function.

Many of the figures are poorly labelled, lack titles, or have incomplete or absent legends, necessitating reference to the text to determine their significance. Nonetheless, the authors have expended much time and effort in the compilation of the data recorded in this text.

ROBERT W. HELLENHORST

Eduard Pernkopf Atlas of Topographical and Applied Human Anatomy, Volume 1. Edited by Helmut Ferner. Translated by Harry Monsen. Baltimore, Urban and Schwartzenberg, Inc., 1980. Hardcover, 302 pages, preface, table of contents, index, 108 black and white figures and 231 full color figures.

This is Volume 1 of a three-volume atlas. The second concerns the thorax, abdomen and extremities, and the third contains the index. This atlas beautifully illustrates the structures of the skull, brain, eye and orbit, and other major sections of the face, the perinasal sinuses, oral cavity, ear, neck, pharynx, and larynx. The section on the skull is well done. It provides valuable correlations between roentgenograms of the skull and their anatomic landmarks. Additionally there are arteriograms of the external carotid artery and its branches and internal carotid angiograms, vertebral angiography, phlebograms, and pneumoencephalograms. Many of the plates are exquisitely diagrammed and labeled and are a joy to study.

Unfortunately, not all of the plates dealing with the eye are accurate. One plate shows the inferior oblique muscle inserting superior to the equator. In another the superior oblique muscle appears to be inserting on the nasal side of the superior rectus muscle. An illustration of the lymph channels of the head shows tractus lymphaticus orbitalis, with anterior as well as posterior orbital lymph drainage. These, however, are but minor points, and they do not subtract from the overall value of the atlas with its fine correlation of radiology and anatomy.

FRANK W. NEWELL

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

American Journal of Roentgenology

CT OF ORBITAL INFECTION AND ITS CEREBRAL COMPLICATIONS. Zimmerman, R. A., and Bilaniuk, L. T. (Dept. Radiol., Hosp. Univ. Pennsylvania, Philadelphia, Pa.). Am. J. Roentgenol. 134:45, 1980.

A group of 18 patients with orbital infection was examined with computed tomography. The most common cause of orbital cellulitis was sinusitis and the second most common cause was trauma. The CT-scan proved to be a very informative method of evaluating orbital infections. It was capable of demonstrating the presence, location, and extent of subperiosteal abscesses, intraorbital foreign bodies and intraconic scarring as well as the cerebral complications of cerebritis, brain abscess, and epidural infection. (9 figures, 1 table, 15 references) —David Shoch

Annals of Neurology

CEREBELLAR CONTROL OF OCULAR GAZE STABILITY. Zee, D. S., Leigh, R. J., and Mathieu-Millaire, F. (Dept. Neurol. and Ophthalmol. , Johns Hopkins Univ. School of Med., Baltimore, Md.). Ann. Neurol. 7:37, 1980.

The ability to hold an eccentric position of gaze has been attributed to a brainstem network termed the ocular motor neural integrator. For this integrator to function properly, an intact cerebellum is necessary. This report describes a patient with cerebellar dysfunction who showed an unusual form of nystagmus: each slow phase had a waveform of increasing velocity. This contrasts with gaze paretic nystagmus, the more typical manifestation of cerebellar disorder, in which each slow phase has a waveform of decreasing velocity. Based on these observations and results from basic research, the authors propose that (1) the cerebellum controls neural integration in the brainstem by a positive feedback loop, and (2) pathological alterations in the strength of transmission (or gain) through the feedback loop cause the eyes to drift off target, with either an exponentially increasing (gain too high) or decreasing (gain too low) velocity. (2 figures, 17 references)—Authors' abstract

Archives of Ophthalmology

THE MODE OF PROGRESSIVE DISC CUPPING IN OCULAR HYPERTENSION AND GLAUCOMA. Pederson, J. E., and Anderson, D. R. (Dept. Ophthalmol., Bascom Palmer Eye Inst., Univ. Miami, Miami, Fla.). Arch. Ophthalmol. 98:490, 1980.

Serial disk photographs of 259 patients with elevated intraocular pressures were studied retrospectively up to 15 years. Twenty-nine eyes showed progressive enlargement of the optic cup. Early vertical extension of the cup occurred in five eyes and horizontal extension in one. In 23 eyes, a generalized expansion of the cup (retaining its round appearance) was the first change observed, typically preceding visual field loss by several years. Thus, serial disk photographs are necessary for the earliest detection of optic nerve damage in ocular hypertension. Of 18 eyes with normal visual fields at the time progression of cupping was first noted, typical glaucomatous field loss developed in 50% during a follow-up of one to six years (average, two years). Therefore, treatment is indicated for eyes exhibiting progressive disc cupping, even in the absence of visual field defects. (9 figures, 2 tables, 34 references)—Authors' abstract

ISCHEMIC OPTIC NEUROPATHY IN CHRONIC PAPILLEDEMA. Green, G. J., Lessell, S., and Loewenstein, J. I. (Depts. Ophthalmol. and Neurol., Boston Univ. School Med., Boston, Mass.). Arch. Ophthalmol. 98:502, 1980.

The authors evaluated the condition of a patient with chronic papilledema due to pseudotumor cerebri in whom a permanent, monocular, inferior, altitudinal, visual field defect suddenly developed. Clinical and fluorescein angiographic findings indicated that the loss of visual field was due to ischemic optic neuropathy. Ischemic optic neuropathy might occur in papilledema if the tissue pressure in the optic

disk becomes sufficiently elevated to occlude the pressure-sensitive prelaminar arterioles. (4 figures, 13 references)—Authors' abstract

Biological Psychiatry

SMOOTH PURSUIT EYE MOVEMENTS AND ATTENTION IN PSYCHIATRIC PATIENTS. Pivik, R. T. (Dept. Psychiatry, Faculty of Health Sci. and School of Psych., Univ. Ottawa, Ottawa, Ontario). Biol. Psychiatry 14:859, 1979.

Three groups of patients were studied for their ability to pursue a moving target. There were approximately 20 patients in each group. One group acted as a control, the second group was out-patients being treated for psychiatric disorders and a third group was in-patients who had more severe psychiatric difficulties. The latter two groups were receiving similar drugs while the control group received no drugs at all. The study shows that the out-patient group and the controls did much better on eye-tracking of a moving target than did in-patients. Drug use is not a factor since the last two groups had used the same drugs and it is concluded that patients with psychiatric difficulties sufficient to warrant hospitalization are much more easily distracted from assigned tasks than either normals or out-patients and that in addition there appears to be a process of information overload which prevents the more severely disturbed patient from pursuing an assigned task. (7 figures, 5 tables, 30 references)—David Shoch

Canadian Journal of Ophthalmology

RENEWAL OF ROD OUTER SEGMENTS FOLLOWING LIGHT-INDUCED DAMAGE OF THE RETINA. Wyse, J. P. H. (Lions Sight Ctr., Div. Morpho. Sci., Univ. Calgary, Calgary). Can. J. Ophthalmol. 15:15, 1980.

Fluorescent lighting was used to induce severe but reversible damage of the rod outer segments of the retinas of albino rats. The animals were then kept in continuous darkness for up to 12 days. Pairs of animals were killed after one, three, five, seven, nine and 12 days of continuous darkness. Light microscopic examination of the retinas demonstrated a sharp demarcation between the light-damaged distal ends of the rod outer segments and the newly formed proximal ends. Measurement of the proximal ends demonstrated proximodistal renewal of the rod outer segments during the first nine days of continuous darkness. Parametric statistical analysis of the data revealed that the renewal occurred linearly, at an average rate of 2.66 micrometers per day, which is similar to the rate of renewal of the rod outer segments in the undamaged retina of the rat. (7 figures, 1 table, 18 references)—Author's abstract

SIALIDOSIS: THE CHERRY-RED SPOT — MYOCLONUS SYNDROME. Kirkham, T. H., Coupland, S. G., and Guitton, D. (Depts. Neurol., Neurosurg., and Ophthalmol., McGill Univ., Montreal). Can. J. Ophthalmol. 15:35, 1980.

The sialidoses are a group of storage disorders of autosomal recessive inheritance in which there is a deficiency of lysosomal neuraminidase (sialidase) activity and associated sialyloligosaccharidiuria. Patients with one type of sialidosis may present initially to the ophthalmologist because of a cherry-red spot at the macula. In most of these patients progressive neurologic deficits ultimately develop; myoclonus is a prominent feature. A patient with the so-called cherry-red spot—myoclonus syndrome is described who had a marked deficit of the ocular smooth pursuit system, with consequent nystagmus. His visual system was normal clinically and electrophysiologically despite the obvious storage in the retinal ganglion cells. (5 figures, 21 references) —Authors' abstract

Clinical Genetics

RETINAL MANIFESTATIONS IN FAMILIAL JUVENILE NEPHRONOPHTHISIS. Godel, V., Iaina, A., Nemet, P., and Lazar, M. (Dept. Ophthalmol., Ichilov Hosp., and Dept. Nephrology, Sheba Med. Ctr., Tel Aviv Univ. Med. School, Israel). Clin. Genet. 16:277, 1979.

Juvenile nephronophthisis and medullary cystic disease are complex renal conditions resulting in early renal failure due to glomerular hyalinization and atrophy of the distal tubules. One of the most frequent extrarenal manifestations in this disorder is retinitis pigmentosa-like retinal degeneration. This paper describes three families with this renal problem. The extrarenal manifestations include congenital Leber amaurosis, retinitis pigmentosa and sector retinitis pigmentosa. This variabil-

ity in the retinal findings is explained by the presence of a pleiotrophic gene with variable expressivity. (3 figures, 15 references) —David Shoch

Journal of the Royal Society of Medicine

NEW TECHNIQUES IN DIAGNOSIS OF EYE MUSCLE PALSIES. Huber, A. (Univ. Eye Clin., Zurich, Switzerland). J. Royal Soc. Med. 73:115, 1980.

Two electrical types of testing have aided greatly in the diagnosis of eye muscle palsies. The first of these is electromyography which facilitates differentiation between myopathies, myasthenias, neurogenic palsies and supranuclear motility disorders. This differentiation is based on the different appearances of the electromyograms at the different levels of involvement. A second valuable aid is oculography which measures the saccadic velocity on one hand and the acceleration on the other. Oculographic measurement of saccadic movement gives a valuable indication of the severity of eye muscle palsy and if repeated can give some indication of the degree of recovery. The combination of electromyography and oculography permits the innervational pattern of eye muscles to be correlated with certain types of eye movements under normal and pathological conditions. (9 figures, 6 references) —David Shoch

Lancet

THE EYE AS A SANCTUARY IN ACUTE LYMPHOBLASTIC LEUKEMIA. Ninane, J., Taylor, D., and Day, S. (Depts. Haematol., and Ophthalmol., Hosp. for Sick Children, London). Lancet 1:452, 1980.

Leukemic infiltration of the anterior chamber of the eye was the only sign of relapse in two children with acute lymphoblastic leukemia who had been off treatment for two and four months. Leukemic infiltration of the eye is rare and usually occurs with simultaneous central nervous system relapse. However, the two patients reported here never had any evidence of central nervous system involvement and their prophylactic irradiation included the posterior pole of the eyes. An alternative explanation is that the leukemic cells were present in the iris at the onset of the disease when blast cells were detectable in the blood and that they were suppressed but not eradicated by chemotherapy. The authors conclude that the anterior segment of the eye may be a sanctuary site in patients with acute lymphoblastic leukemia. The response to radiotherapy is dramatic but this local treatment must be coupled with systemic chemotherapy. (1 figure, 1 table, 11 references) —David Shoch

Medical Journal of Australia

RETINAL MIGRAINE AND THE PILL. Byrne, E. (Royal Adelaide Hosp., Adelaide, S. A.). Med. J. Aust. 2:659, 1979.

After an uneventful pregnancy a young woman began taking a contraceptive pill. Soon afterward she developed paroxysmal, throbbing bifrontal headaches accompanied by nausea. In addition, she complained of photopsia and fortification spectra, with attacks affecting both half-fields on different occasions. Isolated discrete episodes of amaurosis affecting either eye developed at about the same time. An average of two attacks occurred each day. Over a period of three years she had several hundred attacks of transient amaurosis. At this time the pill was stopped and her headaches and visual symptoms ceased although she had one further episode of amaurosis of the left eye six months later. The significance of these findings is that on occasion the migrainous symptoms may herald a cerebral infarction. (12 references) —David Shoch

VISUAL LOSS CAUSED BY CORNEAL CRYSTALS IN MYELOMA. Firkin, F. C., Lee, N., Ramsay, R., and Robertson, I. (Univ. Dept. Med. and Haematology, St. Vincent's Hosp., and Corneal Diseases Unit, Royal Victorian Eye and Ear Hosp., Melbourne, Australia). Med. J. Aust. 2:677, 1979.

Recognition of needle-like crystals in the cornea of a patient with deteriorating visual acuity initiated laboratory studies which demonstrated underlying multiple myeloma. Crystal deposition in the cornea occurs only rarely in multiple myeloma, and evidently reflects an unusual tendency for certain paraproteins to form numerous small aggregates which are deposited particularly within, and between, corneal epithelial cells. Treatment with chemotherapy, plus repeated plasma exchange with a normal plasma protein product resulted in

significant depletion of crystals, and improvement in visual acuity over a period of three weeks. Accelerated clearance of paraprotein by plasmapheresis appeared to contribute materially to the rapidity of recovery, since recovery was considerably faster than in reported cases where treatment was with chemotherapy alone. (2 figures, 6 references) —Authors' abstract

Ophthalmologica

TRABECULECTOMY WITH SCLERAL WICK: TECHNIQUE AND EARLY RESULTS. Kottow, M. H. (Charlottenklinik für Augenkranke, Stuttgart). Ophthalmologica 179:99, 1979.

A variation to standard trabeculectomy is described, whereby the trabecular tissue flap is not completely excised, but dissected free, hinged at its nasal end and sutured diagonally across the scleral bed, to act as a wedge between the scleral flap and its bed, in an attempt to decrease the tendency of the sclera to scar into a watertight barrier. In addition, it is suggested that the trabecular flap acts as a wick that aids in the filtration of the aqueous humour.

The technique has been used in 24 eyes with good to excellent, short-term, post-operative intraocular tension control in all but two patients. Mild complications like transient flat anterior chamber or blood cells in the aqueous occur at rates comparable to other filtering procedures. (1 figure, 1 table, 13 references) —Author's abstract

Ophthalmology

RETINOPATHY IN JUVENILE-ONSET DIABETES OF SHORT DURATION. Frank, R. N., Hoffman, W. H., Podgor, M. J., Joondeph, H. C., Lewis, R. A., Margherio, R. R., Nachazel, D. P., Weiss, H., Christopherson, K. W., and Cronin, M. A. (Kresge Eye Inst., Wayne State Univ., Detroit, Mich.). Ophthalmol. 87:1, 1980.

To study objectively the epidemiology of retinopathy in juvenile-onset diabetes, the authors performed fundus photography and fluorescein angiography, using the Diabetic Retinopathy Study protocol, on 122 juvenile diabetics and 65 demographically similar nondiabetic subjects as the control group. Photographs and angiograms were masked as to subjects' identities and evaluated independently by five retinal subspecialists. There was no retinopathy in control subjects. In diabetics, prevalence of retinopathy increased with the duration of disease, being 0% after zero to four years, 27% for five to nine years, and 71% for more than ten years. Retinopathy also increased in prevalence with age with a sharp rise after age 15. There is indication that age and duration act independently. (6 tables, 16 references) —Authors' abstract

INTRAOCULAR HEMORRHAGE FROM VASCULARIZATION OF THE CATARACT INCISION. Watzke, R. C. (Dept. Ophthalmol., Univ. Iowa, Iowa City, Iowa). Ophthalmol. 87:19, 1980.

In a survey of 58 aphakic eyes examined five to ten years after surgery, 12% had episcleral vessels in the inner aspect of the cataract incision and almost half of these eyes showed evidence of mild intraocular hemorrhage. Analysis of these and 33 other eyes indicates that argon laser treatment is only temporarily effective in preventing intraocular hemorrhage. Limbal cryotherapy is effective in a one- to four-year follow-up. While these vessels are a common cause of transient intraocular hemorrhage in aphakic eyes, serious sequelae are rare and treatment is usually unnecessary. (1 figure, 5 references) —Author's abstract

THE ROLE OF GONIO-PHOTOCOAGULATION IN NEOVASCULARIZATION OF THE ANTERIOR CHAMBER ANGLE. Simmons, R. J., Deppermann, S. R., and Dueker, D. K. (Glaucoma Consultation Ser., Massachusetts Eye and Ear Infirm., Boston, Mass.). Ophthalmol. 87:79, 1980.

Gonio-photocoagulation appears to be of benefit in selected cases of progressive neovascularization of the anterior chamber angle. It is of most use when applied early before permanent complications have ensued. In most cases it should be combined with panretinal photocoagulation although this may be done as a separate procedure. The authors recommend that panretinal photocoagulation be done in patients with progressive anterior segment neovascularization and gonio-photocoagulation be used for those who are developing neovascular glaucoma or for those who have already had panretinal photocoagulation and still have evi-

dence of neovascularization. They further suggest that gonio-photocoagulation might be appropriate prior to cataract removal in eyes with neovascularization and as preparation for glaucoma surgery in this same type of eye. (3 references) —David Shoch

AUTOSOMAL DOMINANT KEARNS-SAYRE SYNDROME. Leveille, A. S., and Newell, F. W. (Dept. Ophthalmol., Univ. Chicago, Chicago, Ill.). Ophthalmol. 87:99, 1980.

External ophthalmoplegia, retinal pigmentary degeneration, and heart block constitute the Kearns-Sayre syndrome. Skeletal muscle weakness, deafness, ataxia and endocrine disturbances also may occur. Of 15 members in two generations of a family with autosomal dominant Kearns-Sayre syndrome, seven showed external ophthalmoplegia, six had electrocardiographic abnormalities, six had limb weakness and six were normal. A deltoid muscle biopsy specimen from one patient contained typical "ragged-red fibers," abnormal lipid accumulation, and mitochrondria increased in size and number, containing inclusions. The study demonstrated: (1) the marked variability in genetic expression; (2) the need to examine family members to discover asymptomatic patients and to establish an otherwise unrecognized hereditary pattern; and (3) the absence of specific and consistent biochemical abnormalities. (5 figures, 4 tables, 32 references) —Authors' abstract

TREATMENT OF OCULAR TOXOPLASMOSIS WITH CLINDAMYCIN AND SULFADIAZINE. Tabbara, K. F., and O'Connor, G. R. (Dept. Ophthalmol., and Francis I. Proctor Foundation, Univ. California, San Francisco, Calif.). Ophthalmol. 87:129, 1980.

Seventeen patients with active toxoplasmic retinochoroiditis were treated for four weeks, seven with clindamycin alone and ten with a combination of clindamycin and sulfadiazine. The follow-up period ranged from six months to four years. Results of the Sabin-Feldman dye test were positive in all patients. Five of the seven patients treated with clindamycin alone showed improvement two weeks after treatment was begun, while eight of the ten patients treated with combined clindamycin and sulfadiazine showed both subjective and objective improvement within ten days and signs of healing within three weeks. Since clindamycin and sulfadiazine operate on unrelated metabolic pathways of *Toxoplasma*, they may act synergistically. A regimen consisting of this combination may be appropriate for the treatment of ocular toxoplasmosis. (1 table, 12 references) —Authors' abstract

ANTIMETABOLITE DRUG THERAPY IN HERPES SIMPLEX. Kaufman, H. E. (Lions Eye Research Lab., LSU Eye Ctr., LSU Medical Ctr., New Orleans, La.). Ophthalmol. 87:135, 1980.

Idoxuridine and adenine arabinoside are less than ideal drugs for the treatment of herpes because of toxicity, only partial efficacy with initial dendritic ulcers, and insufficient antiviral activity to prevent occasional epithelial breakthrough. Trifluorothymidine soon to be released by the FDA for general use, appears to be more effective, curing 97% of ulcers in two weeks, and healing large ameboid ulcers more rapidly. Acycloguanosine, in combination with adenine arabinoside virtually eliminates stromal disease in rabbit eyes. A major advantage of this drug is its apparent lack of systemic toxicity due to its ability to interfere with the replication of virus-infected cells while not harming normal cells. Acycloguanosine should be available as an orally active, highly effective antiviral agent that can be given on an out-patient basis to treat deep infections. A new approach to the prevention of herpes recurrence involves the recognition that some isolates of herpes are mild or avirulent. Initial infection with avirulent virus may protect against virulent infection and yet may not cause disease. If such differences in virulence can be correlated with biochemical differences among the strains, prevention and treatment of herpes may be possible through manipulation of these metabolic pathways or immunization with avirulent virus. (2 figures, 1 table, 35 references) —Author's abstract

Survey of Ophthalmology

RAEDER'S SYNDROME: A CLINICAL REVIEW. Grimson, B. S., and Thompson, H. S. (Dept. Ophthalmol., Univ. North Carolina School of Med., Chapel Hill, N. C.) Surv. Ophthalmol. 24:199, 1980.

Raeder's syndrome or the paratrigeminal syndrome is usually defined as a Horner's syndrome plus periorbital pain. The authors

review the findings in 41 patients and divide the syndrome into three subgroups. Group one includes patients with either multiple parasellar cranial nerve involvement (cranial nerves III, IV, V and VI) or involvement of the second and third or all three divisions of the trigeminal nerve. Group two includes patients with periorbital pain but also a typical history for cluster headaches and group three consists of patients with the same pain history not typical for a cluster headache but who may also have involvement of the first division of the trigeminal nerve only. The first group requires full neuroradiological investigations to rule out parasellar mass lesions such as tumors or aneurysms but the latter two groups have a benign prognosis and do not require immediate neuroradiological investigation. However, these latter two groups must be watched for the development of other nerve palsies which might suggest an abnormality involving or adjacent to the extracranial or intracranial course of the internal carotid artery. (4 figures, 5 tables, 64 references) — David Shoch

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

Send News Items double-spaced to News Editor, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least three months before the date of occurrence.

CORNELL UNIVERSITY MEDICAL COLLEGE: EIGHTH ANNUAL COURSE: ULTRASONIC TOMOGRAPHY OF THE EYE AND ORBIT

The Eighth Annual Course, "Ultrasonic Tomography of the Eye and Orbit" will be held June 26-28, 1980, at Cornell University Medical College, New York, New York. Registration fee is $300 and $150 for residents, fellows and technicians. For further information, write Ms. Mary E. Smith, Course Coordianator, Dept. of Ophthalmology, New York Hospital-Cornell Medical Center, 525 E. 68th St., New York, NY 10021.

UNIVERSITY OF WASHINGTON: ALUMNI-RESIDENT DAY

The University of Washington Ophthalmology Alumni-Resident Day will be held in June 7, 1980 in Seattle. For further information, write Richard P. Mills, M.D., Dept. of Ophthalmology, University of Washington, Seattle, WA 98195.

NATIONAL EYE INSTITUTE AND DARTMOUTH-HITCHCOCK MEDICAL CENTER: CLINICAL VISION RESEARCH: EPIDEMIOLOGIC AND BIOSTATISTICAL APPROACHES

The National Eye Institute and the Dartmouth-Hitchcock Medical Center will hold a course, "Clinical vision research: Epidemiologic and biostatistical approaches," June 23-24, 1980, For further information, write Ms. Catherin M. Beinhauer, Office of Continuing Medical Education, Dartmouth-Hitchcock Medical Center, Hanover, NH 03755.

ROCHESTER EYE INSTITUTE AND DEPARTMENT OF OPHTHALMOLOGY: FIFTH ANNUAL OPHTHALMIC SEMINAR

The Rochester Eye Institute and the Department of Ophthalmology at Park Ridge Hospital will hold the Fifth Annual Ophthalmic Seminar August 15 and 16, 1980 at the Rochester Americana Hotel. The main topic of the two-day course will be "The correction of surgical aphakia." For further information, write Ms. Katherine Sgabelloni, R. N., Coordinator, Ophthalmic Services, Park Ridge Hospital, 1555 Long Pond Road, Rochester, NY 14626.

XIII PAN AMERICAN CONGRESS OF OPHTHALMOLOGY

The XIII Pan American Congress of Ophthalmology will be held May 10-15, 1981, in Acapulco, Mexico. For further information, write Francisco G. Martinez-Castro, M.D., Pan-American Association of Ophthalmology, Apartado Postal 11-566, Mexico 11, D.F. Mexico.

ST. MARY'S HOSPITAL, MONTREAL: STEREOCHRONOSCOPY OF THE OPTIC DISK

A workshop on stereochronoscopy of the optic disk will be held in Bern, Switzerland, Aug. 30, 1980. For further information, write K.E. Schirmer, M.D., St. Mary's Hospital Center, 3830 Lacombe Ave., Montreal, Quebec H3T 1M5 CANADA.

UNIVERSITY OF COLORADO SCHOOL OF MEDICINE AND COLORADO OPHTHALMOLOGICAL SOCIETY: SIXTY-SIXTH ANNUAL POSTGRADUATE COURSE

The University of Colorado School of Medicine and the Colorado Ophthalmological Society will present the sixty-sixth annual postgraduate course entitled "Problems in pediatric ophthalmology" course in Vail, Colorado July 7-10, 1980. Registration fee is $150. For further information, write Office of Postgraduate Medical Education, University of Colorado School of Medicine, 4200 E. Ninth Ave., Denver, CO 80262.

UNIVERSITY OF UTAH: ORBITAL UPDATE COURSE

The University of Utah Division of Ophthalmology will sponsor an orbtial update course Sept. 19, 1980, in Snowbird, Utah.

For further information, write George E. Sanborn, M.D., Division of Ophthalmology, University of Utah Medical Center, 50 N. Medical Dr., Salt Lake City, UT 84132.

Cornell University Medical College: First Combined Alumni Meeting

The first combined alumni meeting of the Department of Ophthalmology of Cornell University Medical College will be held June 5-7, 1980, at the New York Blood center in New York City . Registration fee is $225 and $100 for residents and fellows. For further information, write Ms. Mary E. Smith, Course Coordinator, Dept. of Ophthalmology, New York Hospital-Cornell Medical Center, 525 E. 68th St., New York, NY 10021.

University of Texas: Ophthalmology Two-Day Clinical Conference

The University of Texas Health Science Center at San Antonio will sponsor a two-day ophthalmology clinical conference, June 26 and 27, 1980. For further information, write the Office of Continuing Education Services, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284.

Appeal For Autopsy Material From Amblyopic Humans For Morphological Study

It is now known that there are easily detectable and measurable morphological changes in the lateral geniculate nuclei of animals deprived of normal vision in early postnatal life. From this work have come many basic concepts of clinical relevance with regard to amblyopia caused by strabismus, congenital cataracts, and high refractive errors.

However, the brain of a human amblyopic has never been studied post mortem. Such specimens are urgently needed to determine the clinical consequences of ongoing basic research. As amblyopia is never a fatal disease, the old ocular abnormalities are usually forgotten when an autopsy is performed. We appeal to ophthalmologists to become aware of the need to obtain brain tissue when one of their patients with a history of amblyopia, congenital or infantile cataracts, or unilateral corneal opacities since infancy comes to autopsy. Fixation of the posterior thalamus including the lateral geniculate nuclei and the occipital lobes including the visual cortex in 10% formalin would suffice for our purposes and the tissue should be sent to one of the following: Gunter K. von Noorden, M.D., Baylor College of Medicine, Department of Ophthalmology, Texas Children's Hospital, P. O. Box 20269, Houston, TX 77025; telephone (713) 791-3183; or Laurence J. Garey, M.D., Ph.D., Institute of Anatomy, Rue du Bugnon 9, 1001 Lausanne, Switzerland: telephone (021) 23 22 62.

The Society of Heed Fellows

The Heed Foundation was established in 1945 by Thomas D. Heed, to support postresidency ophthalmic education. Recipients have formed a Society of Heed Fellows that meets annually at the American Academy of Ophthalmology meeting. There are currently 378 members of the Society of Heed Fellows.

Each year the Society selects a member who has made an outstanding contribution to ophthalmology. Past recipients of the Award are: Stuart I. Brown, Goodwin M. Breinin, Matthew D. Davis, J. Terry Ernest, Milton Flocks, Froncie Gutman, Eugene Helveston, William F. Hoyt, Philip Knapp, Paul R. Lichter, Harvey A. Lincoff, Marvin H. Quickert, William H. Spencer, William S. Tasmen, and George O. Waring.

At the 1979 meeting, the Heed Fellows donated a gift of $10,000 to the Heed Foundation in appreciation for the support provided by the Foundation. The Heed Ophthalmic Foundation will use these funds to augment the support of future Heed Fellows.

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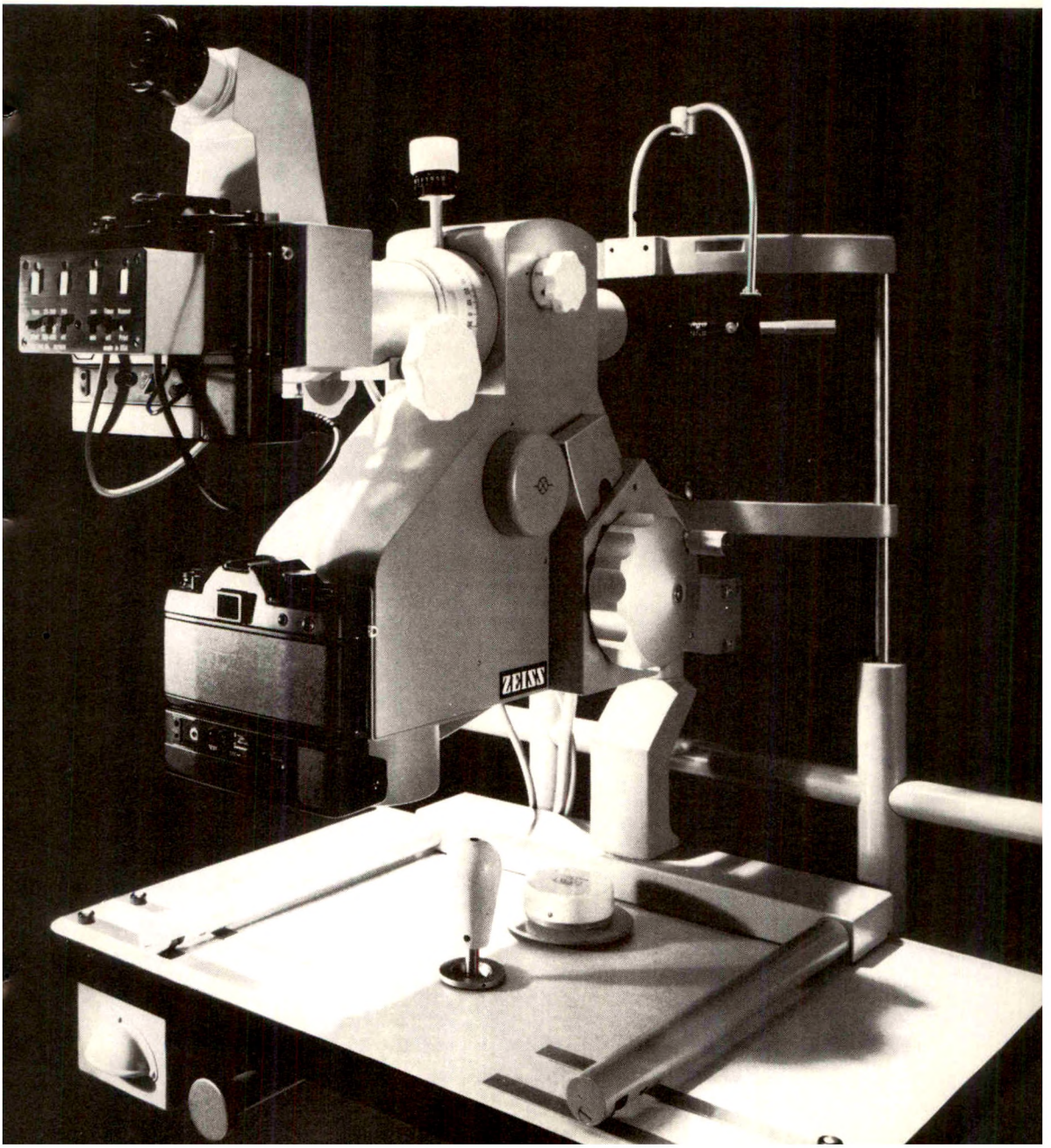

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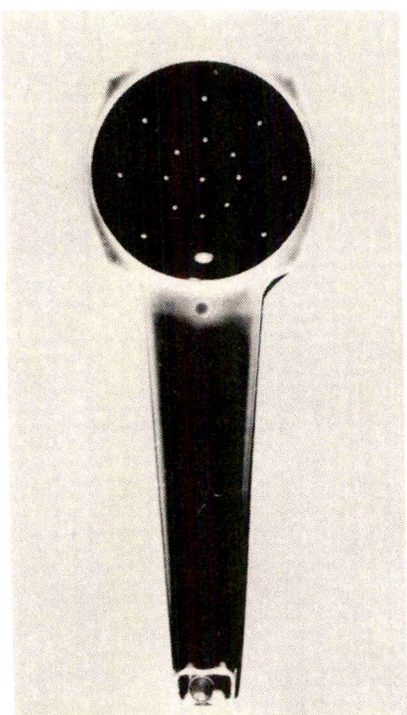
Tuition is $875.00. For further information and application forms, please write to J. W. Bettman, M.D., Division of Ophthalmology, A-227, Stanford Medical Center, Stanford, California 94305.



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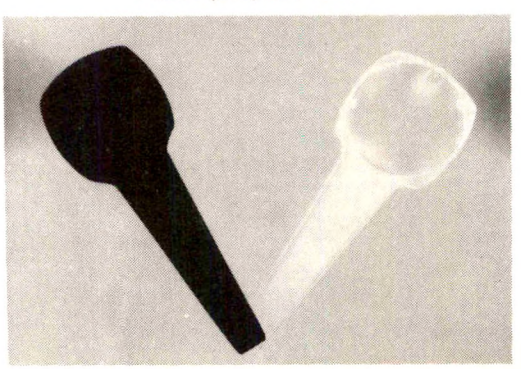

WHEN THE DOCTOR DIES

You will probably need to know these items:

1. Social Security Number or Taxpayer's Identification Number
2. Accountant or Estate Planner: Name, address, phone number
3. Attorney: Name, address, phone number
4. Employee(s): Name(s), address(es), phone number(s), details of termination of services
5. Insurance Agent (and/or Estate Planning Manager): Name, address, phone number
6. Stockbroker: Name, address, phone number
7. Trust (if established): Name of Trustee, address, phone number, name of bank's representative, phone, extension if the trustee is a bank
8. Will: Location, location of any codicils
9. Home: Location of deed, mortgage papers, etc.
10. Office: Location of deed or lease, mortgage papers, duration of lease or mortgage, provision for settling in event of death
11. Other real estate: Location(s) of deed(s) or mortgage paper(s)
12. Life Insurance: Location of policies
13. Other Insurance: Location of policies
14. Temporary coverage of the Practice: Name, address and phone number of an associate
15. Securities: Location of policies
16. Current unpaid bills: Location
17. Outstanding obligations: Notes, mortgages, pledges, charge accounts, credit checking accounts, etc. Details
18. Safety Deposit Box(es): Location(s), number(s), location of keys
19. Savings Account(s): Location(s) of passbook(s)
20. Checking Account(s): Location(s), location(s) of checkbook(s)
21. Financial Records: Location
22. Cash: Location of receipts, unbanked cash, source of cash for immediate needs
23. Tax Information: Location
24. Accounts Receivable: Location, the Doctor's views on collecting current and delinquent bills
25. Notes, loans, mortgages, etc., due from others: Location of items
26. Notifying patients: Method preferred by the doctor, location of appointment book
27. Notification: Hospital(s)—(Administrator), phone numbers: colleagues, phone numbers, Societies, etc., phone numbers
28. Veterans Administration: Branch of Service, date of discharge, service number, VA number(s), location of discharge papers
29. Blue Cross, etc.: Policy numbers of Blue Cross, Blue Shield and other Health Insurance (see later discussion)
30. Narcotics: Location of drugs, tax stamp, narcotics ledger, narcotics order book
31. Equipment (major): Purchase price, sales outlet
32. The Doctor's views on disposition of property, securities, anticipated income, etc.
33. Birth and Marriage Records: Location
34. Citizenship Papers (if applicable): Location

In addition to the foregoing but subject to the rights and duties of the Executor or Administrator, you may become involved with the following:

I. Probate of the Will: Your attorney will do this.

II. Disposition of narcotics, drug samples and medications. You should contact your Regional Office of the Bureau of Narcotics and Dangerous Drugs, U.S. Department of Justice, requesting disposition forms which must be completed and returned.

III. Patient Records:

A. These are important and confidential records which should be carefully preserved. Apparently there is no set limit of time specified by law.

B. The contents of such records should be disclosed to another physician only if the patient so requests. Such a request should be in writing and should be retained with the records. Normally, the records are confidential and diagnostic information in them should not be disclosed directly to the patient because of the risk that he might misinterpret them.

C. All patients' medical records should be kept for a minimum of ten years. Records of patients who were minors when treated should be preserved until two years after the patient reaches twenty-one. When possible, records should be kept for twenty-five years. It should be kept in mind that requirements for the retention of medical records may vary from state to state. Accordingly, before any medical records are destroyed or disposed of, local requirements should be verified with either the attorney for the estate or the local medical society. Financial records should be kept for five years, which is the statute of limitations on such information.

IV. Telephone: If there is an answering service, this can be a very helpful way of notifying patients of the Doctor's death with possible suggestions regarding their continued care. It is suggested that this service be retained for at least a month.

V. Notifying patients: Perhaps a simple sign on the office door "Call ———————— (office phone number)" will relieve you of the burden of contact with most of the patients and the answering service can take care of the matter.

If the physician's secretary is retained temporarily she might perform this service by being present during usual office hours. She also could notify patients with future appointments during this time.

VI. Taxes: The accountant and/or attorney should take care of all of this in connection with the financial records.

VII. Stopping advertising mail: It may take a year for knowledge of the Doctor's death to reach all the mailing lists; there is no central clearing office. You may perhaps choose to let it run out in this fashion, or you may write "Deceased return to sender" on each piece and mail it back. While the latter course might entail some effort initially, it will rapidly and effectively cut off the flow.

VIII. Insurance Agent and/or Trustee: A preliminary brief conference might be in order to settle the question of immediate funds, documents to be located, and arrangements for a later, detailed conference. Prompt notification of such people is important.

IX. Consideration of Sale of Practice: If the practice is to be sold, with or without real estate, relatively rapid action is advised, for it will quickly lose value. It can be advertised in the State Medical "Journal" and the "Journal" of the American Medical Association.

X. Real Estate: Except for practice-connected real estate, a hasty decision on sale or retention is not advised. It is hoped that the doctor has made known his views on this subject.

XI. Temporary coverage of patients:

A. Some arrangement with a colleague should be made immediately as regards patients in the hospital.

B. While not required, it would be a courtesy to be able to suggest a colleague to other patients.

XII. Insurance:

A. Malpractice Insurance: A refund on unused premiums may be possible. Find the policy and consult the local agent.

B. Liability and other Insurances: Certain policies issued with reference to the practice might have provisions for refund of unused premiums. Consult the issuing company or your insurance agent.

C. Health and Hospital Insurance: The survivor of a physician who had hospital or other health insurance under a group or family plan may keep such insurance, but it should be transferred to individual instead of family policies, unless you have dependent children.

XIII. Veterans Administration: If the Doctor was a Veteran, notify the Veterans Administration with the indicated information and apply for deserved benefits. Help with this can be had through the Veteran's Service Officer of the Doctor's county or district, or the Veterans Administration Regional Office. In this connection, save the Doctor's discharge papers permanently. It is possible that Pensions or other forms of remuneration may be provided in the future.

XIV. Social Security: Nearly all physicians are now covered by the Social Security Act. Visit the Social Security Office serving your area to find out what benefits are available to you. Be certain to have the Doctor's Social Security or Taxpayer Identification Number.

XV. Automobile(s): Title, if in Doctor's name, can be transferred with assistance of an automobile club, if a member, or through the Department of Motor Vehicles. Be sure insurance coverage is retained.

XVI. Equipment: It is best disposed of as part of the practice, if possible. Otherwise, it might be possible to obtain an estimate of value from one of the reputable equipment vendors and then sold either privately, through an advertisement in the State Medical "Journal" or to a dealer of used equipment. One of the Doctor's colleagues can give you the names of the major supply dealers serving your area.

XVII. Current bills: These must be paid, but not until the court has approved the Executor or appointed the Administrator of the Doctor's estate.

XVIII. Magazine subscriptions: Those purchased for office use might be checked for possible stoppage and subscription refund if you do not wish to continue them.

XIX. Dues: There is ordinarily no refund on Medical Society dues unless hardship exists.

XX. Securities: It is worth noting that Securities can be used as collateral for loans to meet financial needs. This may be preferable to selling the securities.

The American Society of Internal Medicine has learned with regret of the Doctor's death. We wish to extend our condolences. We realize that you will have many tasks in connection with settlement of the estate. To assist you the Society has prepared this pamphlet.

It should be pointed out that many of the items appearing herein are matters which, technically, will be the professional responsibility of the Executor (if the Doctor died with a Will) or the Administrator (if the Doctor died without a Will). However, the information contained herein may prove to be helpful not only to the person having this responsibility but also to the Doctor's survivor. We recommend that the survivor discuss the contents of this pamphlet with the Executor or Administrator of the Doctor's estate as soon as possible.

REPRINTED WITH PERMISSION FROM THE AMERICAN SOCIETY OF INTERNAL MEDICINE. THIS BROCHURE WAS PREPARED BY THE NORTH CAROLINA SOCIETY OF INTERNAL MEDICINE AND THE CLEVELAND (OHIO) ACADEMY OF MEDICINE.

INTRAOCULAR MICROSURGICAL WORKSHOP

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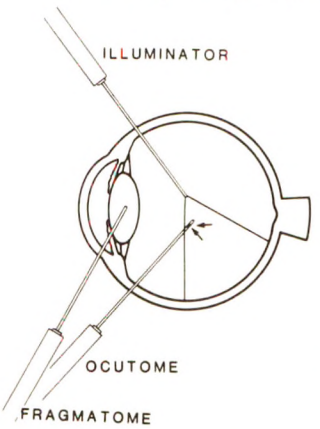

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Howard Kohn, M.D.
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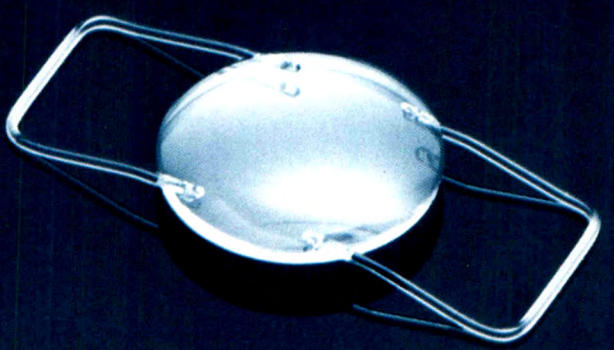

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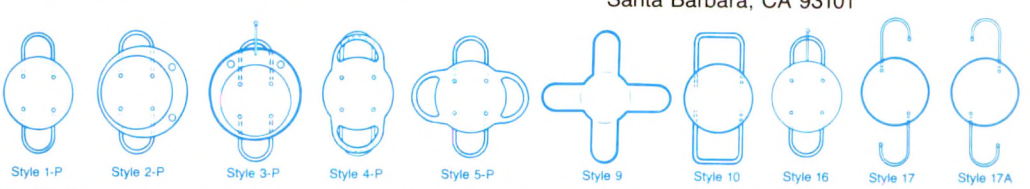

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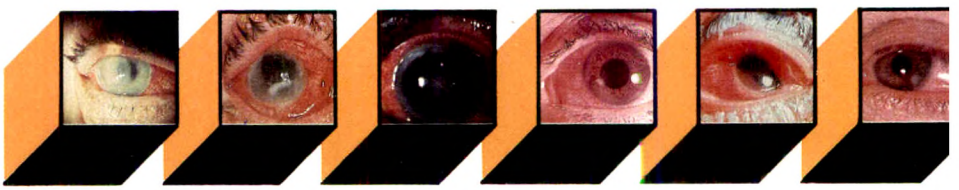

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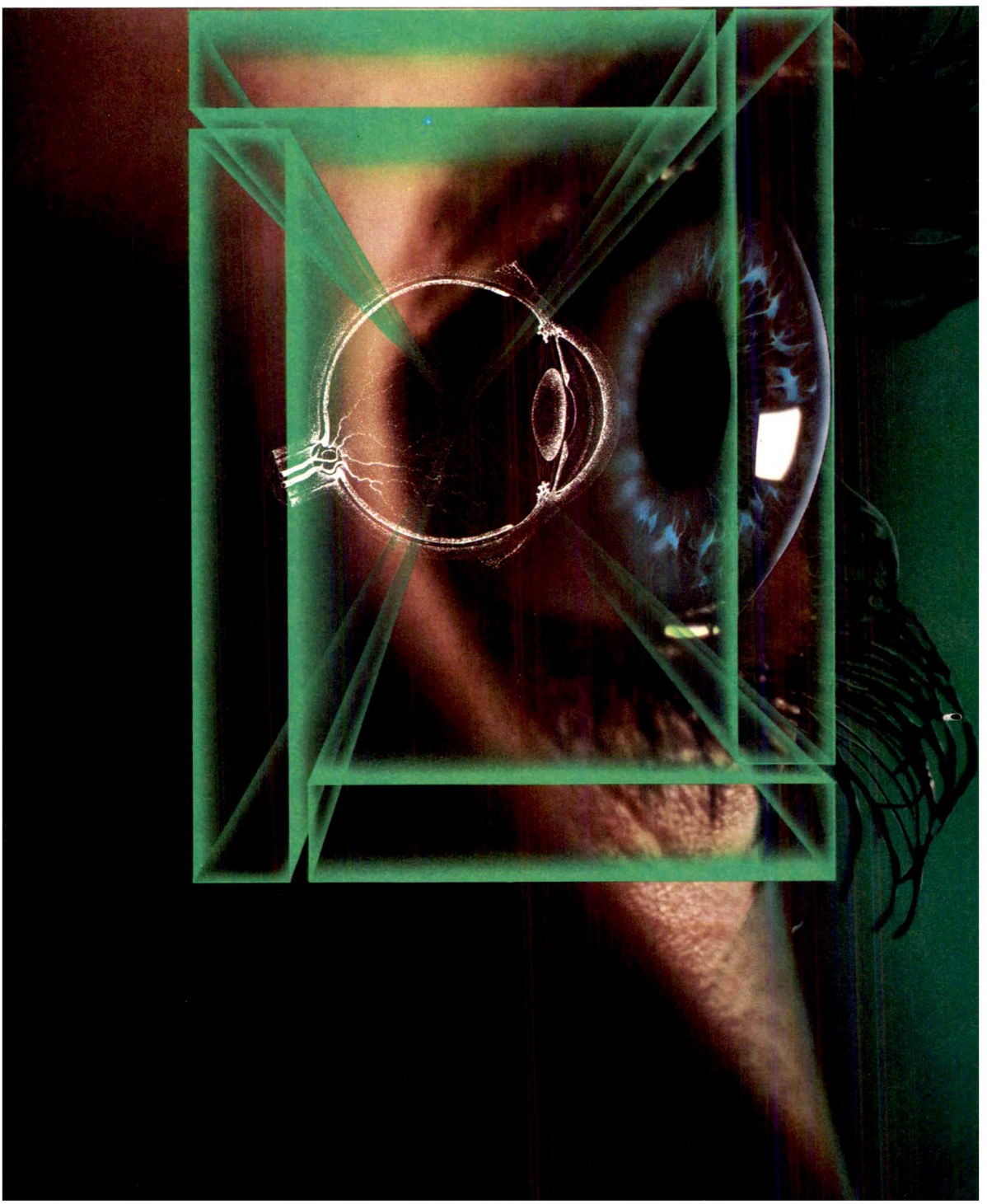

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1. Data on file at Alcon Laboratories.
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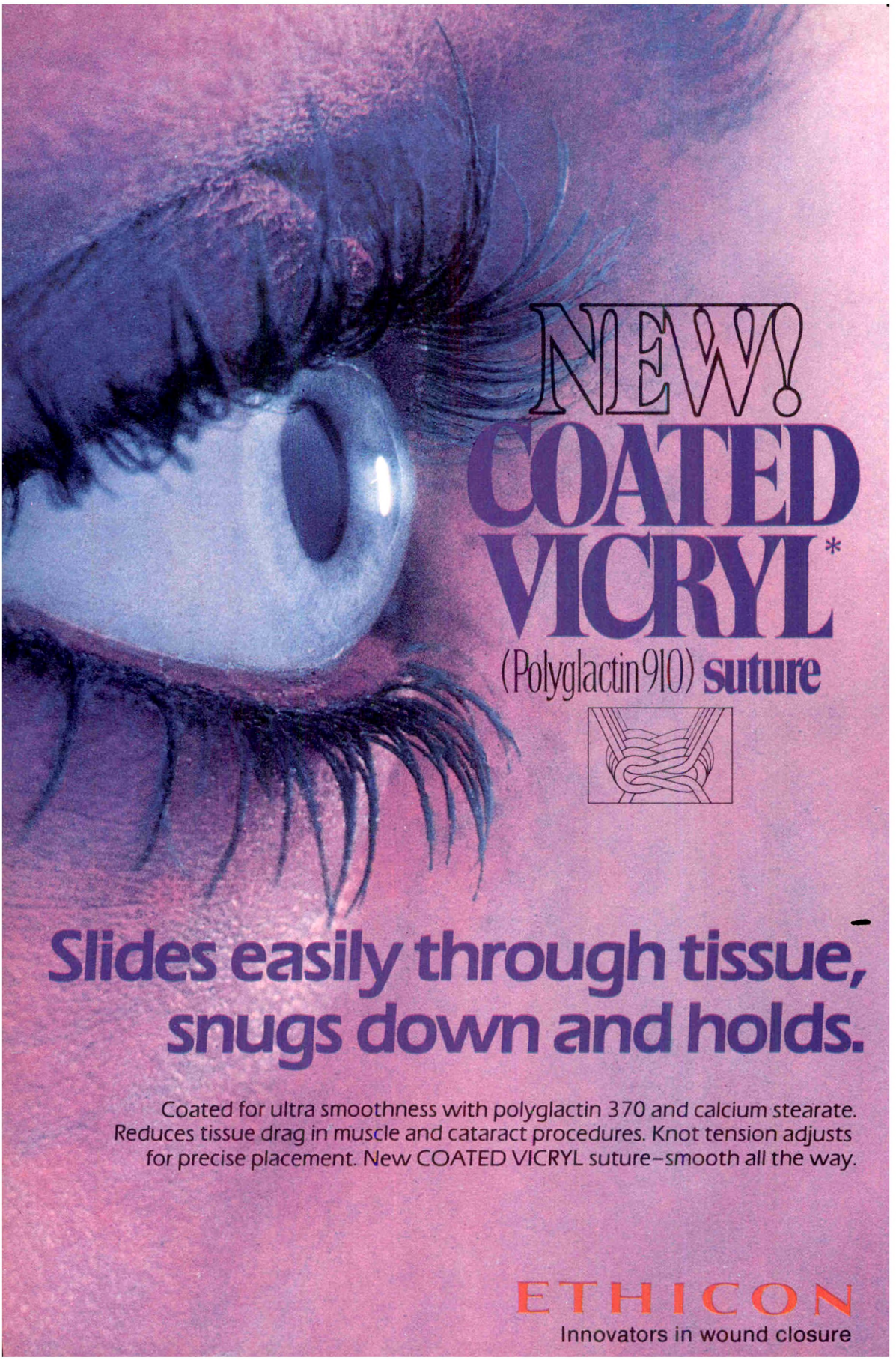
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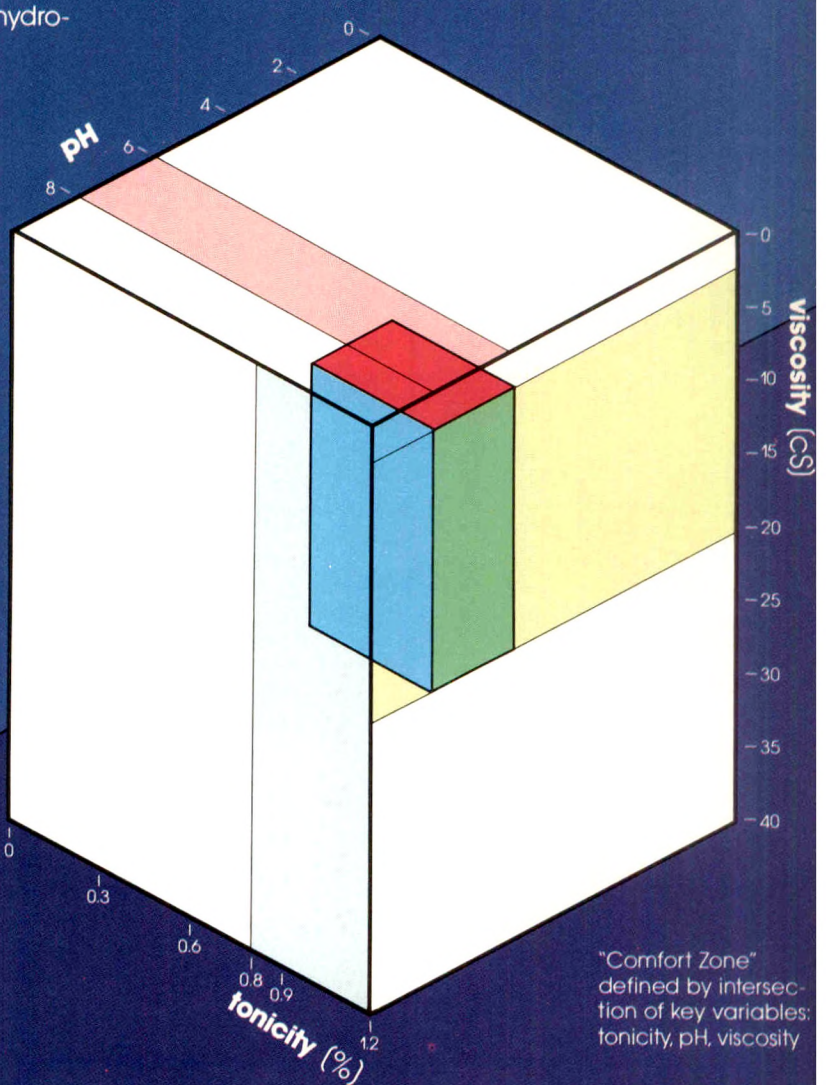

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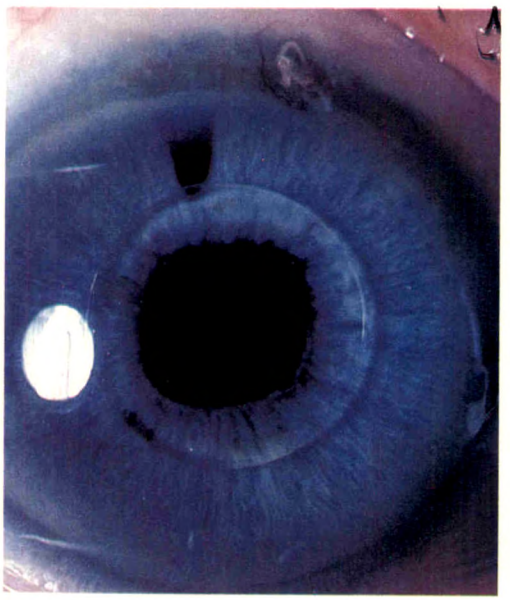

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Nelson, EL. Ophthalmic Steroids in Ocular Anti-Inflammatory Therapy. HE Kaufman, Editor, Springfield, ILL. Thomas, 1970.

Hull, FW and Epstein, WA. Comparison of the intraocular pressure effects of topical dexamethasone and fluorometholone. Allergan Report Series No. 74, 1972.

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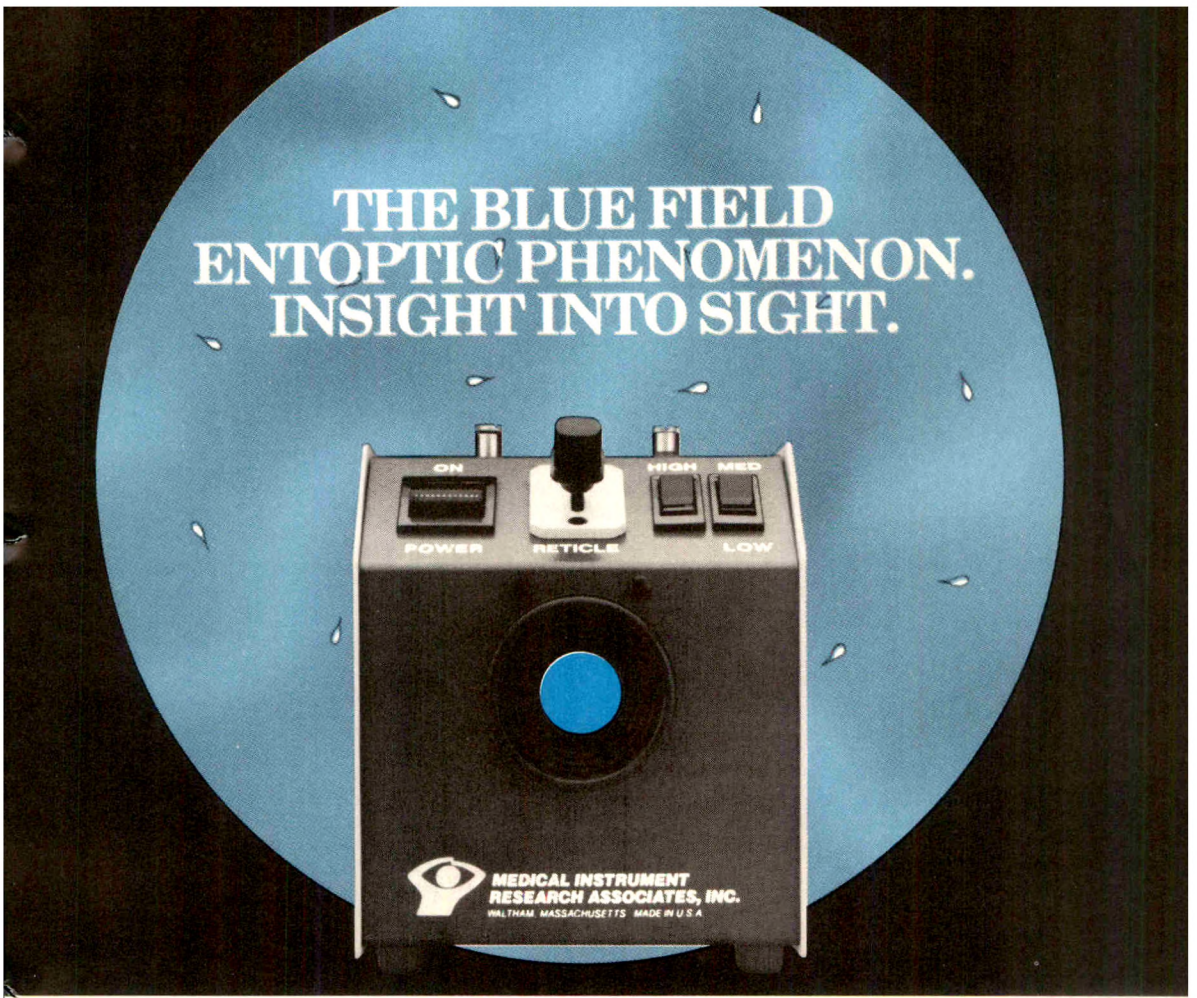

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[1] Sinclar, S., Riva, E., Loebl, M.: Blue field entoptic phenomenon in cataract patients. Archives of Ophthalmology 97: 1092, 1979.

[2] Ibid.

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VIRA-A®
(vidarabine ophthalmic ointment), 3%

Description. Vira-A (vidarabine, adenine arabinoside, or Ara-A) is an antiviral drug for topical ophthalmic administration. The chemical name is 9-β-D-arabinofuranosyladenine. Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

Clinical Pharmacology. Vira-A is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Except for Rhabdovirus and Oncornavirus, Vira-A does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

The antiviral mechanism of action has not been established. Vira-A appears to interfere with the early steps of viral DNA synthesis. Vira-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of Vira-A. Because of the low solubility of Vira-A, trace amounts of both Vira-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of Vira-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, Vira-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, Vira-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit.

Indications and Usage. Vira-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. Vira-A is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions to idoxuridine have occurred. The effectiveness of Vira-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous Vira-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone, have been administered concurrently with Vira-A Ophthalmic Ointment, 3%, without an increase in adverse reactions.

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If Vira-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

Vira-A is not effective against RNA virus or adenoviral ocular infections. Vira-A is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Contraindication. Vira-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. ***Use in Pregnancy:*** Vira-A (vidarabine) parenterally is teratogenic in rats and rabbits. Ten percent Vira-A ointment applied to 10% of the body surface during organogenesis induce fetal abnormalities in rabbits. When 10% Vira-A ointment was ap plied to 2 to 3% of the body surface of rabbits, no fetal abnor malities were found. This dose greatly exceeds the total recom mended ophthalmic dose in humans. The possibility of embryoni or fetal damage in pregnant women receiving Vira-A (vidarabin ophthalmic ointment), 3%, is remote. The topical ophthalmic dos is small, and the drug relatively insoluble. Its ocular penetration i very low. However, a safe dose for a human embryo or fetus ha not been established. Consequently, Vira-A should be used onl when clearly indicated.

It is not known whether Vira-A is excreted in human milk. As a general rule, because many drugs are excreted in human milk nursing should not be undertaken while a patient is under treat ment. However, excretion of vidarabine in breast milk is unlikely because Vira-A is rapidly deaminated in the gastrointestinal traci

Mutagenic Potential: Results of *in vitro* experiments indicate that vidarabine can be incorporated into mammalian DNA and can induce mutation in mammalian cells (mouse L5178Y cell line). Thus far, *in vivo* studies have not been as conclusive, but there is some evidence (dominant lethal assay in mice) that vidarabine may be capable of producing mutagenic effects in male germ cells.

It has also been reported that vidarabine causes chromosome breaks and gaps when added to human leukocytes *in vitro*. While the significance of these effects in terms of mutagenicity is not fully understood, there is a well-known correlation between the ability of various agents to produce such effects and their ability to produce heritable genetic damage.

Oncogenic Potential: Chronic parenteral (IM) studies of vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant increase in liver tumor incidence among the vidarabine-treated females. In the same study, some vidarabine-treated male mice developed kidney neoplasia. No renal tumors were found in the vehicle-treated control mice or the vidarabine-treated female mice.

In the rat study, intestinal, testicular, and thyroid neoplasia occurred with greater frequency among the vidarabine-treated animals than in the vehicle-treated controls. The increases in thyroid adenoma incidence in the high-dose (50 mg/kg) males and the low-dose (30 mg/kg) females were statistically significant.

Hepatic megalocytosis, associated with vidarabine treatment, has been found in short- and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.

The recommended frequency and duration of administration should not be exceeded (see Dosage and Administration).

Precautions. The diagnosis of keratoconjunctivitis due to Herpes simplex virus should be established clinically prior to prescribing Vira-A Ophthalmic Ointment, 3%.

Patients should be forewarned that Vira-A Ophthalmic Ointment, 3%, like any ophthalmic ointment, may produce a temporary visual haze.

Although viral resistance to Vira-A has not been observed, this possibility may exist.

Adverse Reactions. Lacrimation, foreign-body sensation, conjunctival injection, burning, irritation, superficial punctate keratitis, pain, photophobia, punctal occlusion, and sensitivity have been reported with Vira-A Ophthalmic Ointment, 3%. The following have also been reported but appear disease-related: uveitis, stromal edema, secondary glaucoma, trophic defects, corneal vascularization, and hyphema.

Overdosage. Acute massive overdosage by oral ingestion of the ophthalmic ointment has not occurred. However, the rapid deamination to arabinosylhypoxanthine should preclude any difficulty. The oral LD_{50} for vidarabine is greater than 5,020 mg/kg in mice and rats. No untoward effects should result from ingestion of the entire contents of a tube.

Overdosage by ocular instillation is unlikely because any excess should be quickly expelled from the conjunctival sac. Too frequent administration should be avoided.

Dosage and Administration. Administer approximately one half inch of Vira-A Ophthalmic Ointment, 3%, into the lower conjunctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or complete re-epithelialization has not occurred by 21 days, other forms of therapy should be considered. Some severe cases may require longer treatment.

After re-epithelialization has occurred, treatment for an additional seven days at a reduced dosage (such as twice daily) is recommended in order to prevent recurrence.

How Supplied. N 0071-3677-07 (Stock 18-1677-139)

Vira-A Ophthalmic Ointment, 3%, is supplied sterile in ophthalmic ointment tubes of 3.5 g. The base is a 60:40 mixture of solid and liquid petrolatum. **UK**

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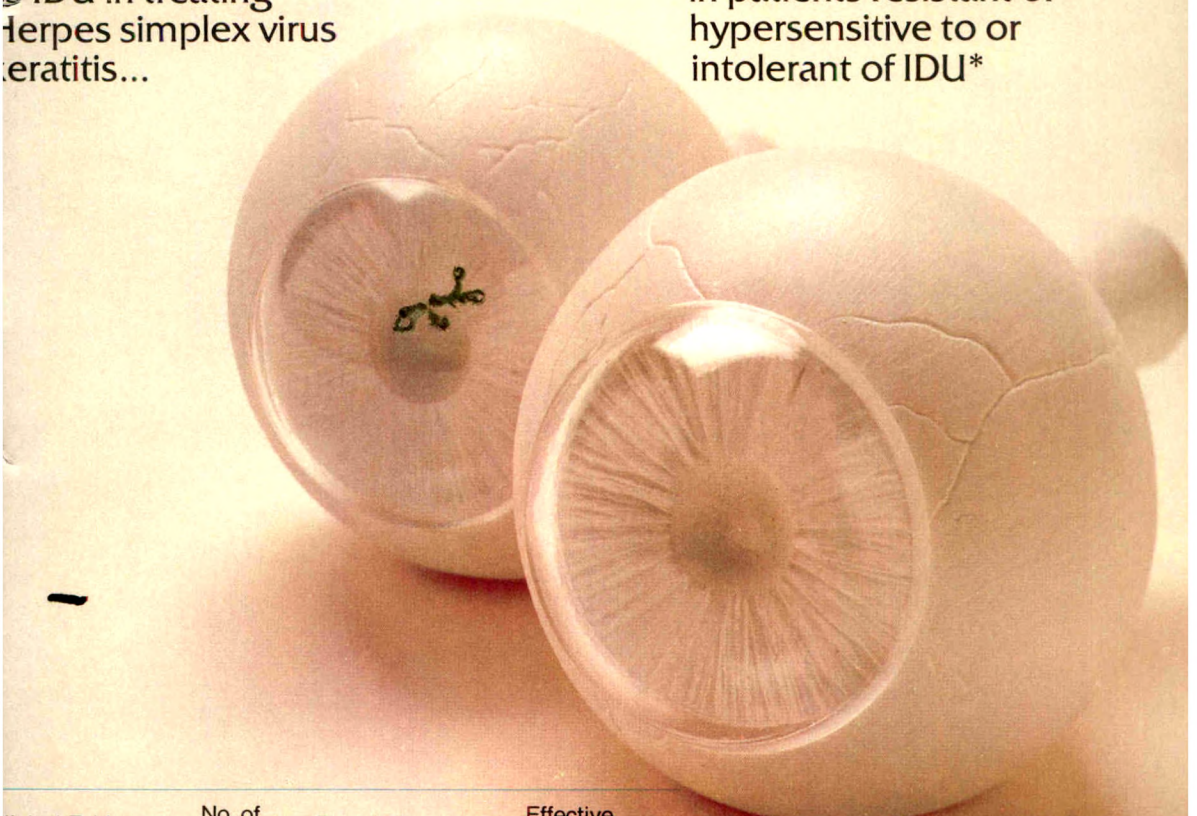

Clinical Evidence	No. of Subjects	Description	Effective Response
Vira-A Controlled Trials	81	Previously untreated	70 subjects **(86%)**
Vira-A Uncontrolled Trials	142	75% had been resistant or hypersensitive to IDU	101 subjects **(71%)**

NOTE: In the controlled and uncontrolled trials, 70 and 101 subjects, respectively, re-epithelialized at the end of three weeks on Vira-A.

*Data on file, Medical Department, Parke-Davis

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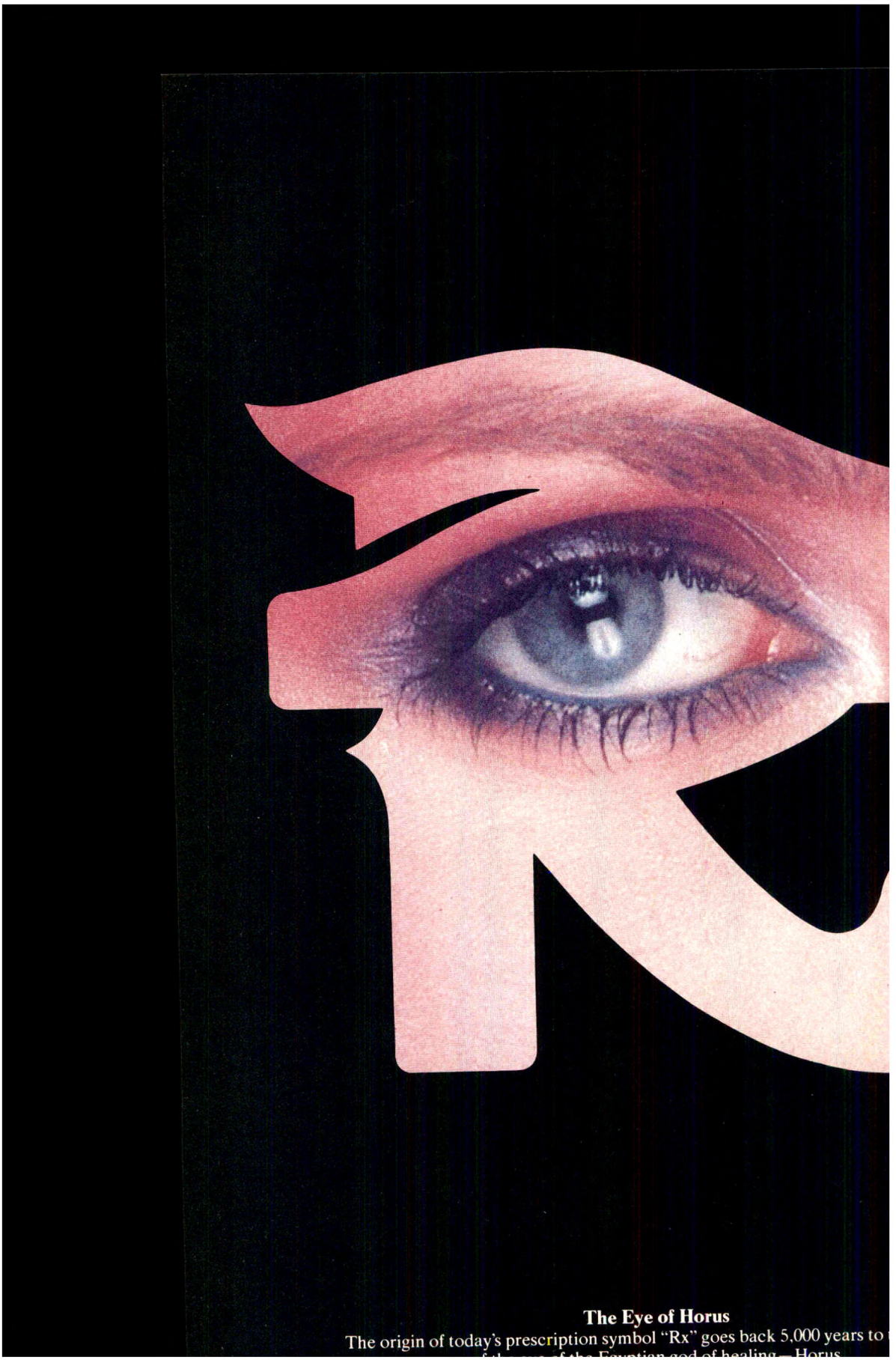

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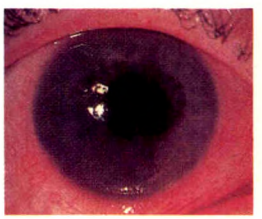

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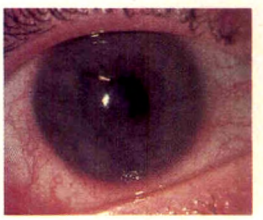

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VIROPTIC®
(Trifluridine)
OPHTHALMIC SOLUTION, 1%
STERILE

DESCRIPTION: VIROPTIC® is the brand name for trifluridine (also known as trifluorothymidine, F_3TdR,F_3T), an antiviral drug for topical treatment of epithelial keratitis caused by Herpes simplex virus. The chemical name of trifluridine is 5-trifluoromethyl-2′-deoxyuridine.

VIROPTIC sterile ophthalmic solution contains 1% trifluridine in an aqueous solution with acetic acid and sodium acetate (buffers), sodium chloride, and thimerosal 0.001% (added as a preservative).

CLINICAL PHARMACOLOGY: Trifluridine is a fluorinated pyrimidine nucleoside with *in vitro* and *in vivo* activity against Herpes simplex virus, types 1 and 2 and vacciniavirus. Some strains of Adenovirus are also inhibited *in vitro*.

Intraocular penetration of trifluridine occurs after topical instillation of VIROPTIC into human eyes. Decreased corneal integrity or stromal or uveal inflammation may enhance the penetration of trifluridine into the aqueous humor. Unlike the results of ocular penetration of trifluridine *in vitro*, 5-carboxy-2′-deoxyuridine was not found in detectable concentrations within the aqueous humor of the human eye.

INDICATIONS AND USAGE: VIROPTIC brand Trifluridine Ophthalmic Solution, 1% is indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus, types 1 and 2. VIROPTIC is also effective in the treatment of epithelial keratitis that has not responded clinically to the topical administration of idoxuridine or when ocular toxicity or hypersensitivity to idoxuridine has occurred. In a smaller number of patients found to be resistant to topical vidarabine, VIROPTIC was also effective.

The clinical efficacy of VIROPTIC in the treatment of stromal keratitis and uveitis due to Herpes simplex or ophthalmic infections caused by vacciniavirus and Adenovirus has not been established by well-controlled clinical trials. VIROPTIC has not been shown to be effective in the prophylaxis of Herpes simplex virus keratoconjunctivitis and epithelial keratitis by well-controlled clinical trials. VIROPTIC is not effective against bacterial, fungal or chlamydial infections of the cornea or nonviral trophic lesions.

During controlled multicenter clinical trials, 92 of 97 (95%) patients (78 of 81 with dendritic and 14 of 16 with geographic ulcers) responded to VIROPTIC therapy as evidenced by complete corneal re-epithelialization within the 14 day therapy period. In these controlled studies, 56 of 75 (75%) patients (49 of 58 with dendritic and 7 of 17 with geographic ulcers) responded to idoxuridine therapy. The mean time to corneal re-epithelialization for dendritic ulcers (6 days) and geographic ulcers (7 days) was similar for both therapies. In other clinical studies, VIROPTIC was evaluated in the treatment of Herpes simplex virus keratitis in patients who were unresponsive or intolerant to the topical administration of idoxuridine or vidarabine. VIROPTIC was effective in 138 of 150 (92%) patients (109 of 114 with dendritic and 29 of 36 with geographic ulcers) as evidenced by corneal re-epithelialization. The mean time to corneal re-epithelialization was 6 days for patients with dendritic ulcers and 12 days for patients with geographic ulcers.

CONTRAINDICATIONS: VIROPTIC brand Trifluridine Ophthalmic Solution, 1%, is contraindicated for patients who develop hypersensitivity reactions or chemical intolerance to trifluridine.

WARNINGS: The recommended dosage and frequency of administration should not be exceeded (see Dosage and Administration).

PRECAUTIONS:

General: VIROPTIC brand Trifluridine Ophthalmic Solution, 1% should be prescribed only for patients who have a clinical diagnosis of herpetic keratitis.

VIROPTIC may cause mild local irritation of the conjunctiva and cornea when instilled but these effects are usually transient.

Although documented *in vitro* viral resistance to trifluridine has not been reported following multiple exposure to VIROPTIC, the possibility exists of viral resistance development.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Mutagenic Potential. Trifluridine has been shown to exert mutagenic, DNA damaging and cell transforming activities in various standard *in vitro* test systems, and clastogenic activity in *Vicia faba* cells.

Although the significance of these test results is not clear or fully understood, there exists the possibility that mutagenic agents may cause genetic damage in humans.

Oncogenic Potential. The oncogenic potential of trifluridine is unknown at this time. The oncogenic potential of trifluridine in rodents is being evaluated.

Pregnancy: The drug should not be prescribed for pregnant women unless the potential benefits outweigh the potential risks.

Nursing Mothers: It is unlikely that trifluridine is excreted in human milk after ophthalmic instillation of VIROPTIC because of the relatively small dosage ($\leq$5.0 mg/day), its dilution in body fluids and its extremely short half-life (approximately 12 minutes). The drug should not be prescribed for nursing mothers unless the potential benefits outweigh the potential risks.

ADVERSE REACTIONS: The most frequent adverse reactions reported during controlled clinical trials were mild, transient burning or stinging upon instillation (4.6%) and palpebral edema (2.8%). Other adverse reactions in decreasing order of reported frequency were superficial punctate keratopathy, epithelial keratopathy, hypersensitivity reaction, stromal edema, irritation, keratitis sicca, hyperemia, and increased intraocular pressure.

OVERDOSAGE: Overdosage by ocular instillation is unlikely because any excess solution should be quickly expelled from the conjunctival sac.

Acute overdosage by accidental oral ingestion of VIROPTIC has not occurred. However, should such ingestion occur, the 75 mg dosage of trifluridine in a 7.5 ml bottle of VIROPTIC is not likely to produce adverse effects. Single intravenous doses of 15-30 mg/kg/day in children and adults with neoplastic disease produce reversible bone marrow depression as the only potentially serious toxic effect and only after 3-5 courses of therapy. The acute oral LD_{50} in the mouse and rat was 4379 mg/kg or higher.

DOSAGE AND ADMINISTRATION: Instill one drop of VIROPTIC Ophthalmic Solution, 1% onto the cornea of the affected eye every two hours while awake for a maximum daily dosage of nine drops until the corneal ulcer has completely re-epithelialized. Following re-epithelialization, treatment for an additional seven days of one drop every four hours while awake for a minimum daily dosage of five drops is recommended.

If there are no signs of improvement after seven days of therapy or complete re-epithelialization has not occurred after 14 days of therapy, other forms of therapy should be considered. Continuous adminsitration of VIROPTIC for periods exceeding 21 days should be avoided because of potential ocular toxicity.

HOW SUPPLIED: VIROPTIC Ophthalmic Solution, 1% is supplied as a sterile ophthalmic solution in a plastic Drop-Dose® dispenser bottle of 7.5 ml.

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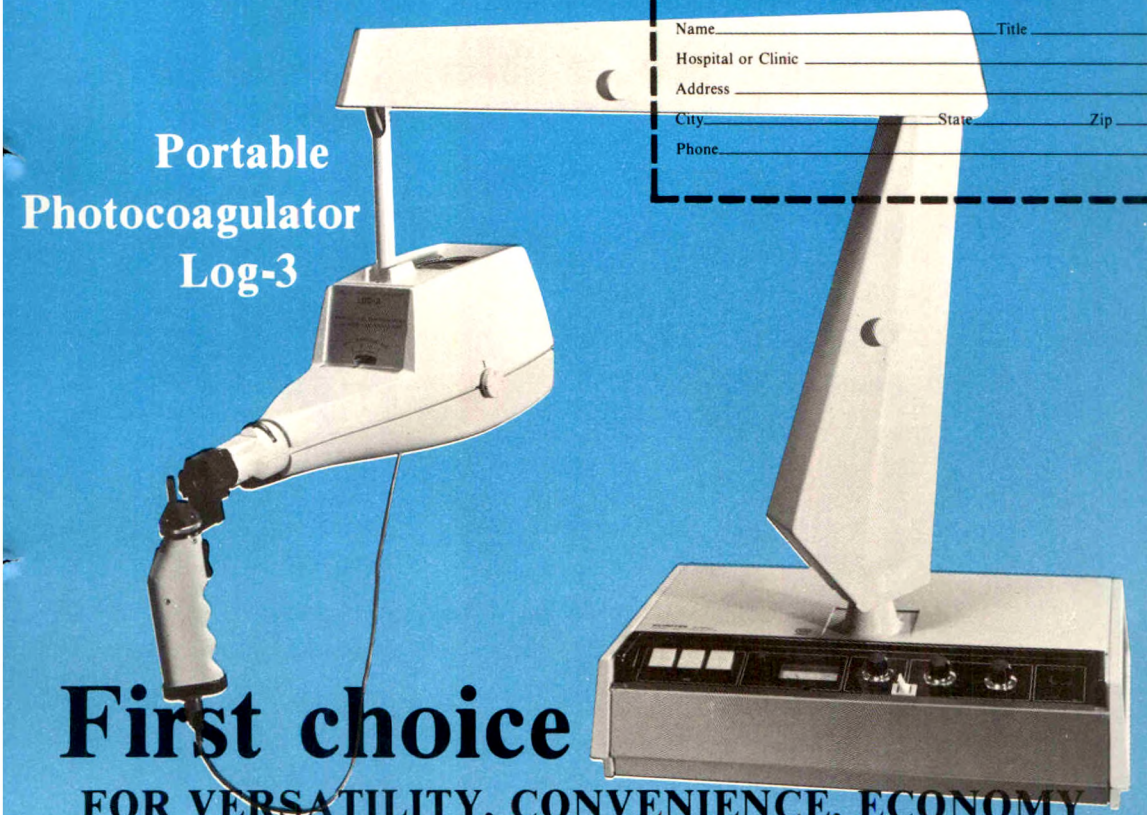

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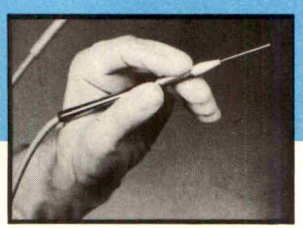

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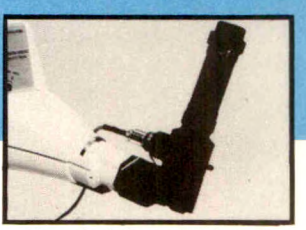

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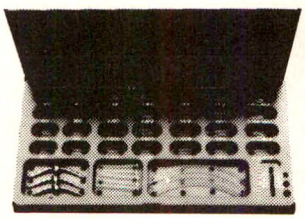

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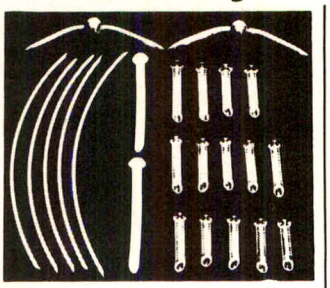

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* L.T. Jones M.D., Dacryocystorhinostomy, American Journal of Ophthalmology, Volume 59, No. 5, May, 1965.
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L.T. Jones M.D. and J.L. Wobig M.D., Surgery of the Eyelids and Lacrimal System, Aesculapius Publishing Company, 1976.

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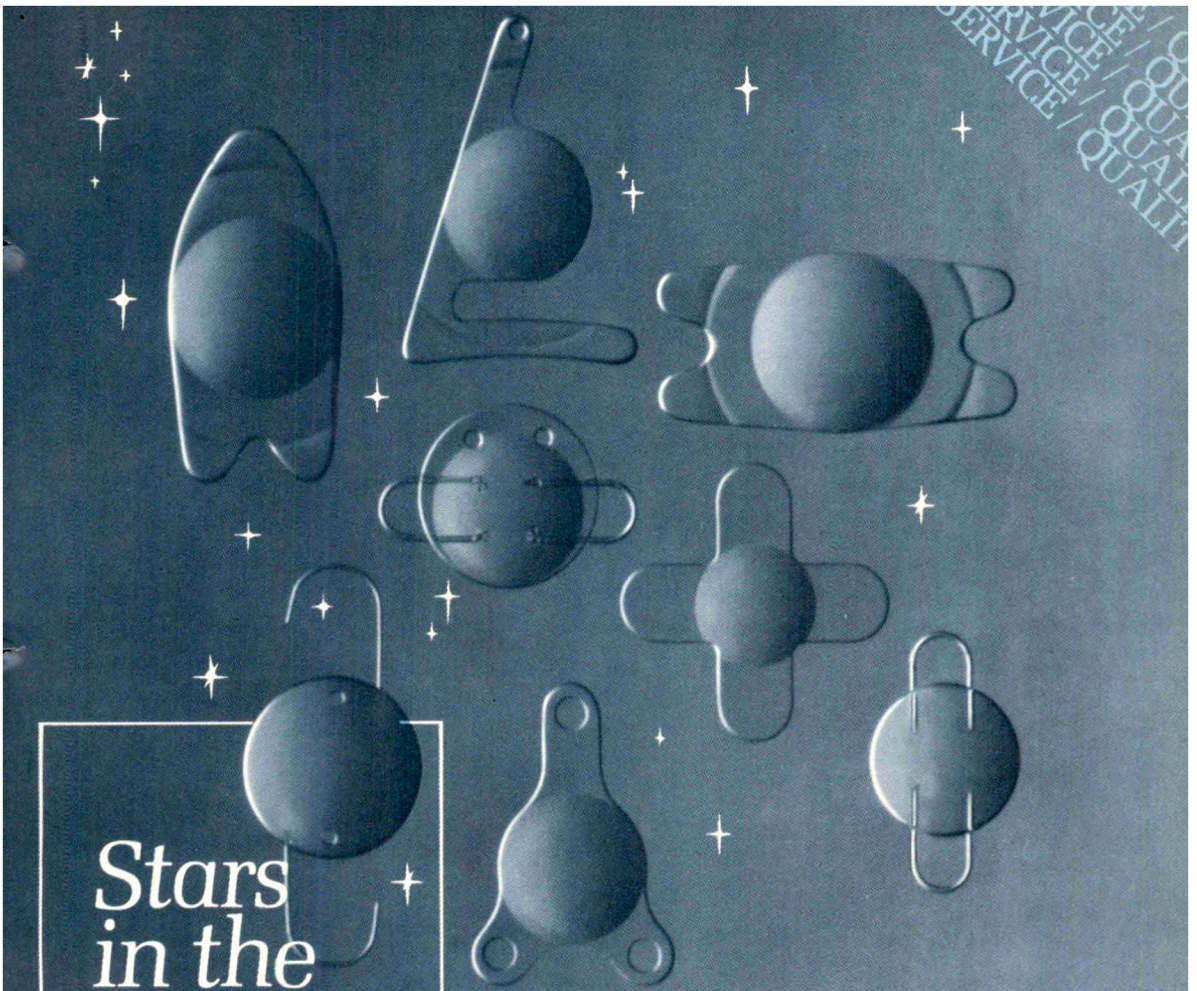

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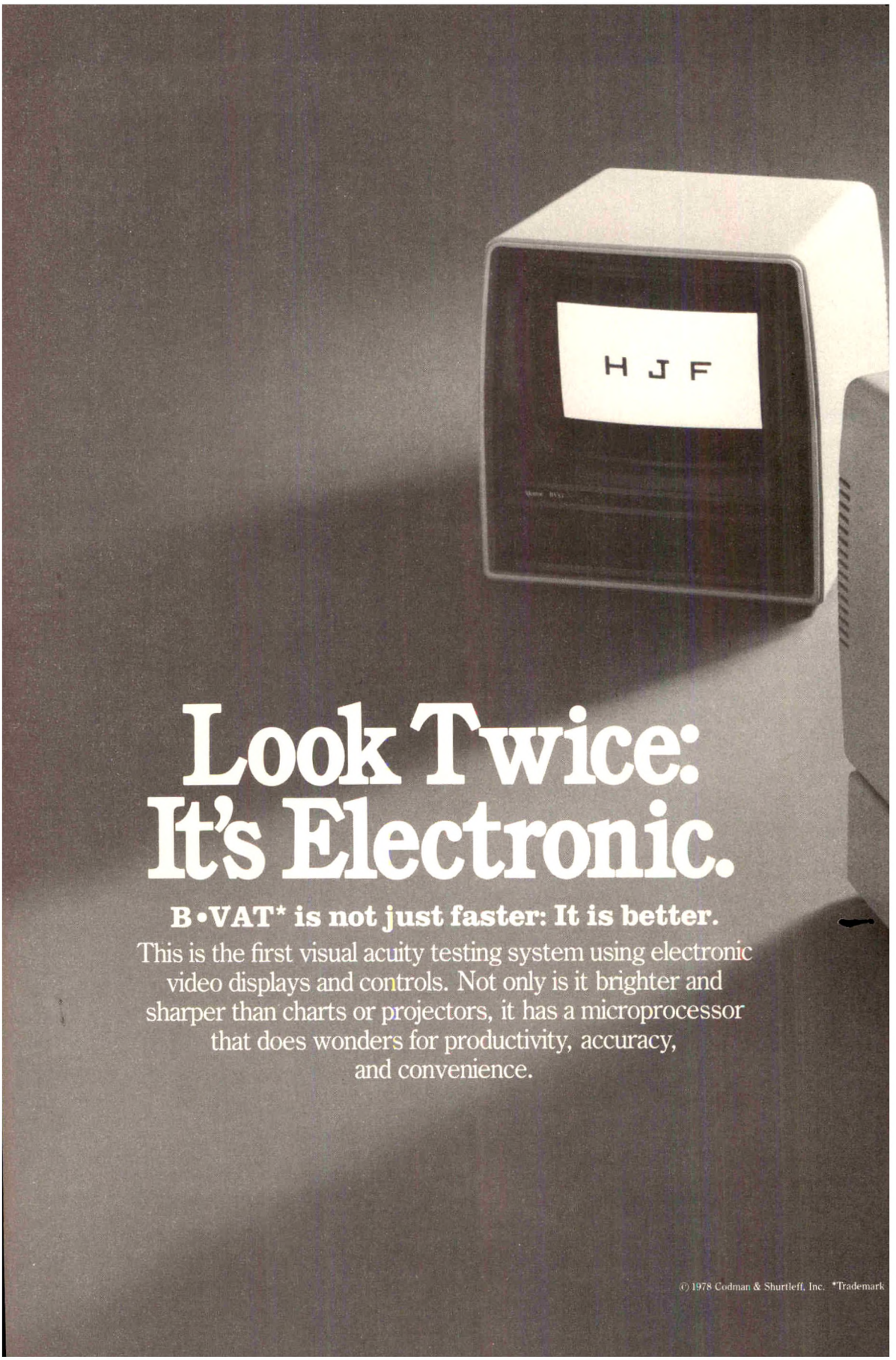

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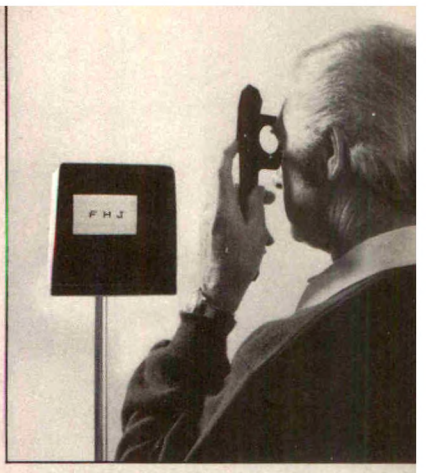

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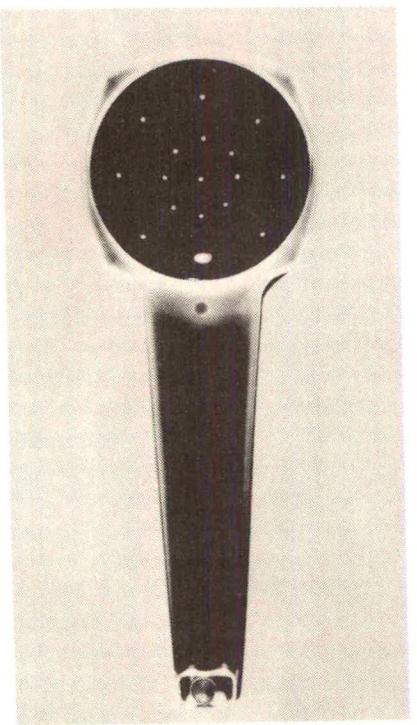

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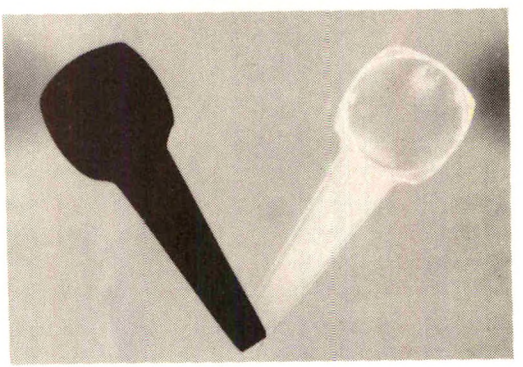

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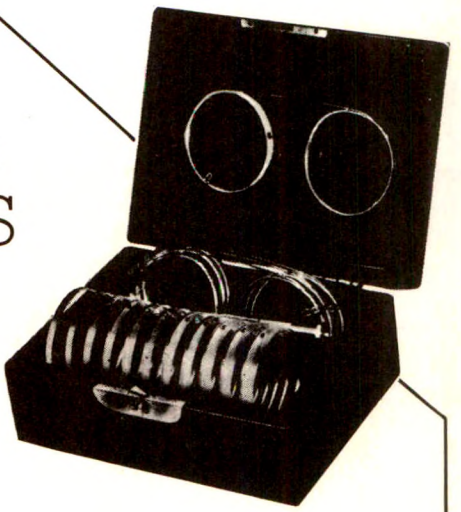

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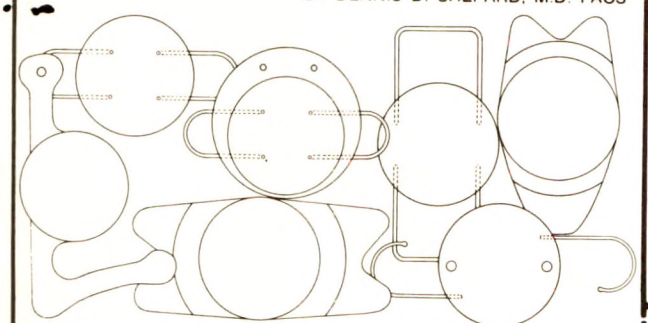

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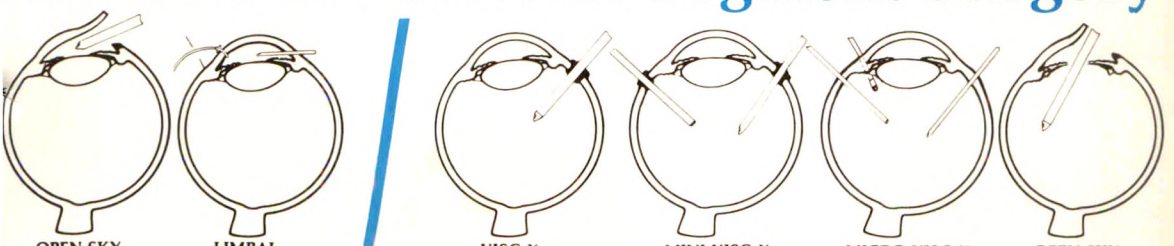

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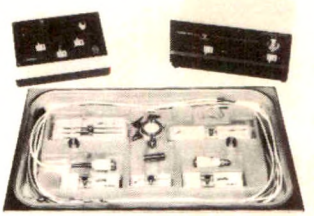

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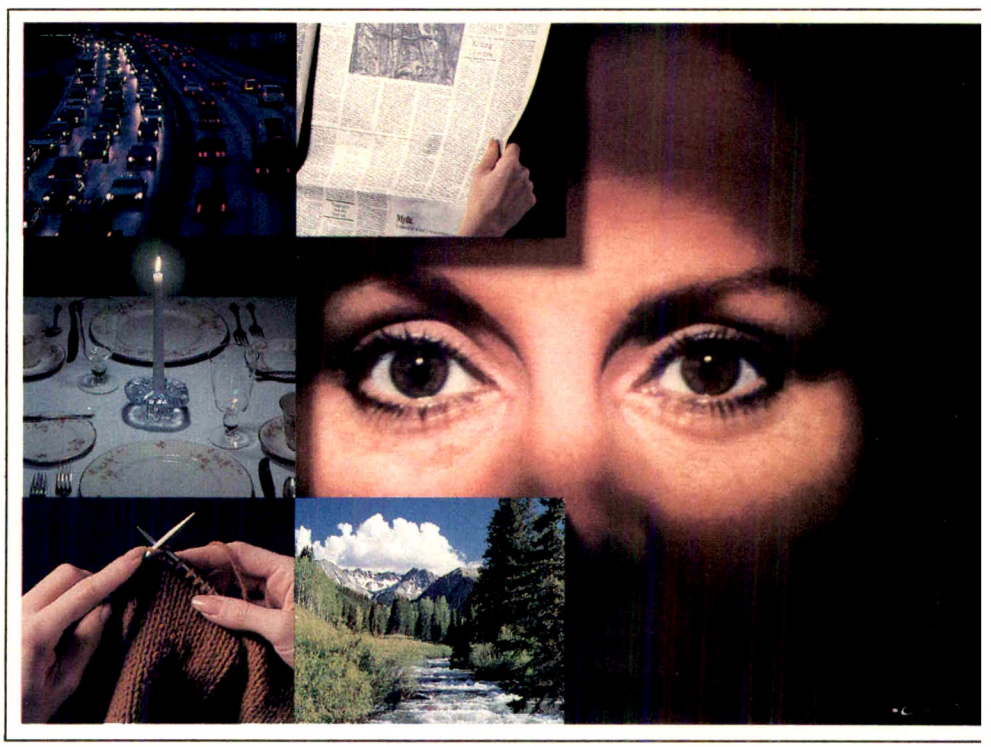

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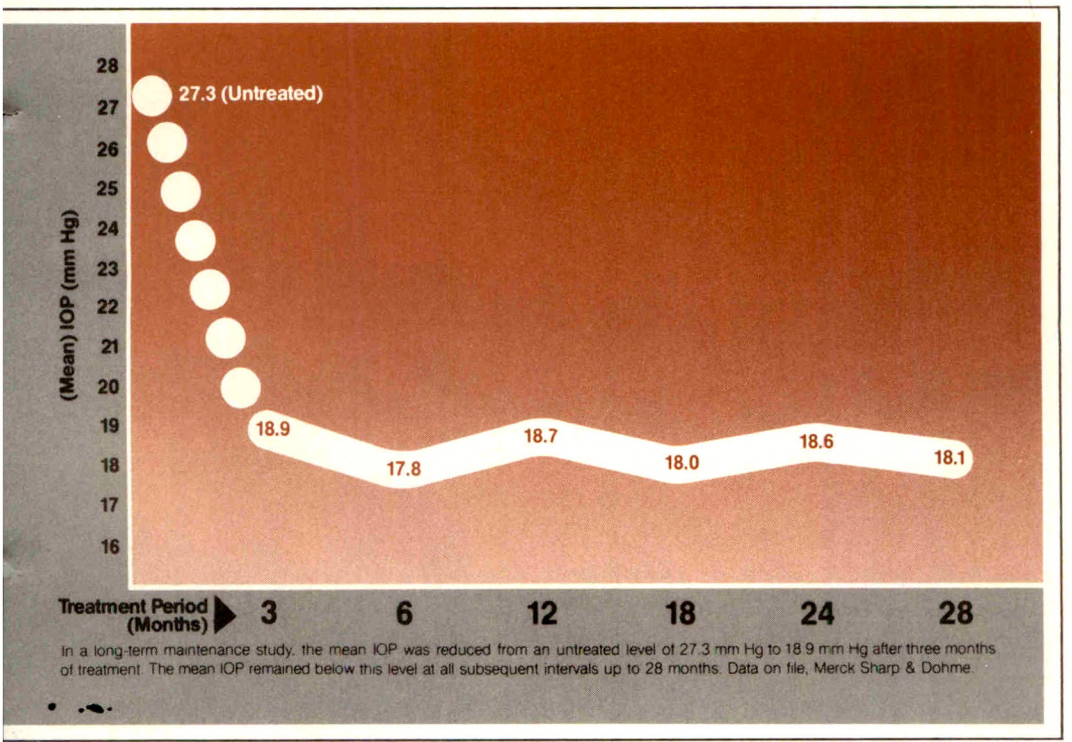

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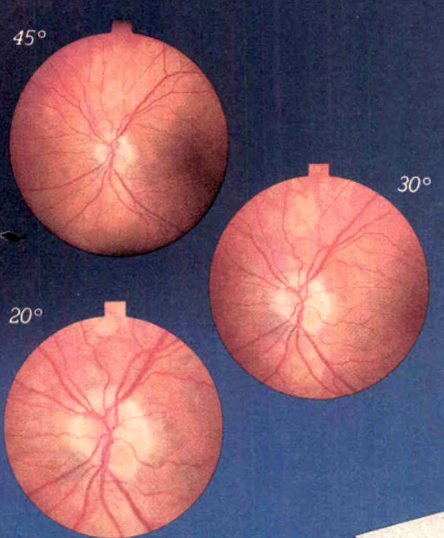

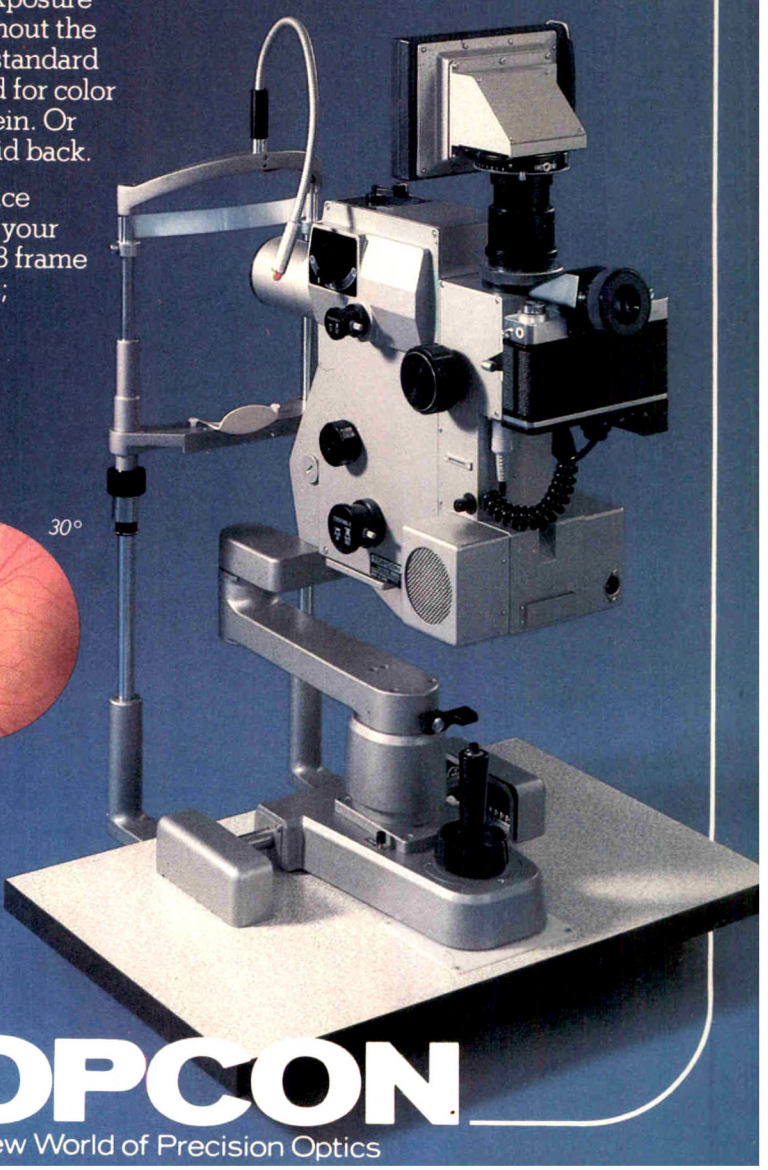

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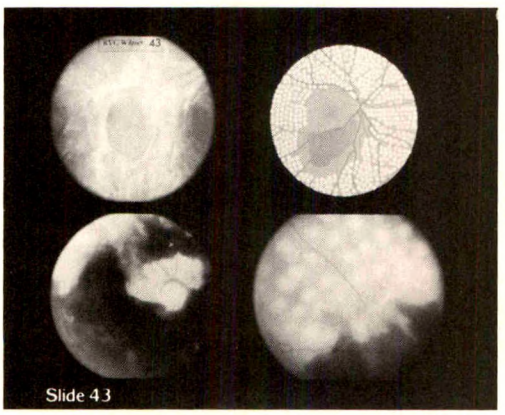

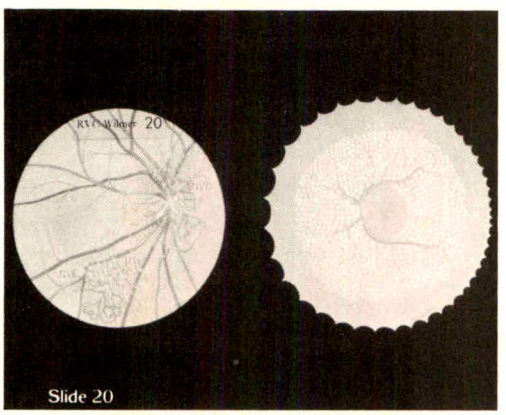

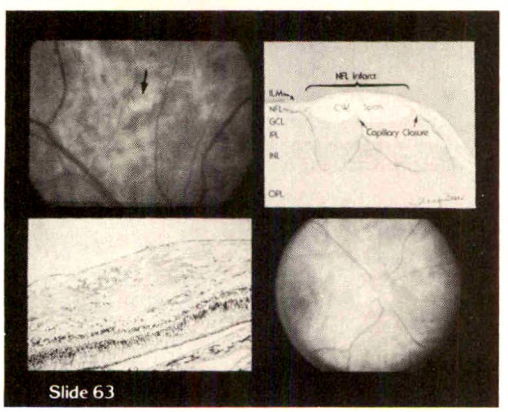

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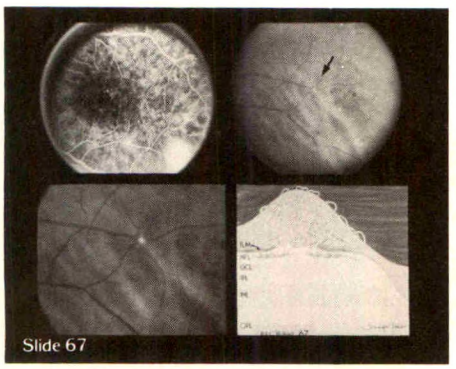

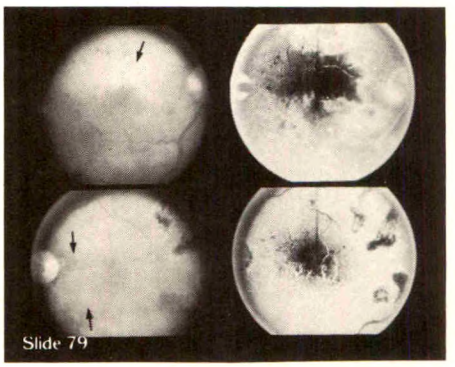

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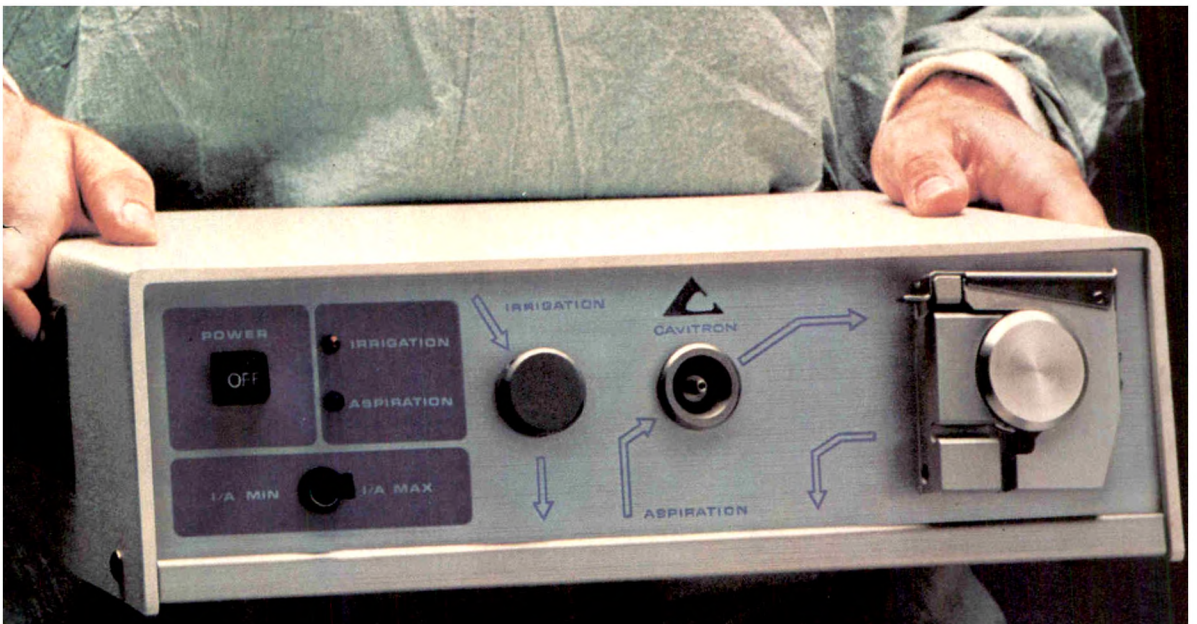

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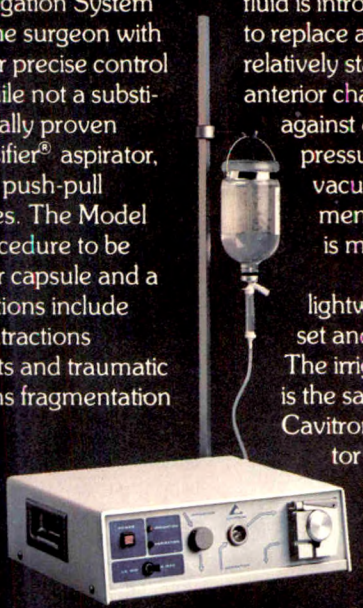

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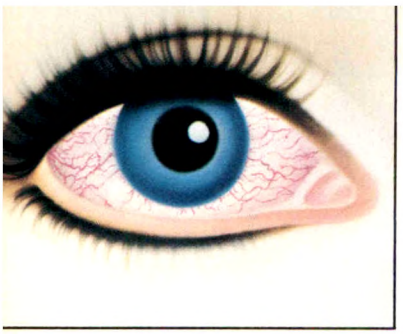

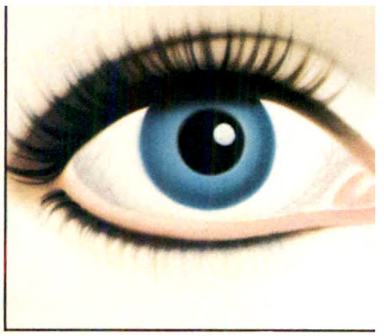

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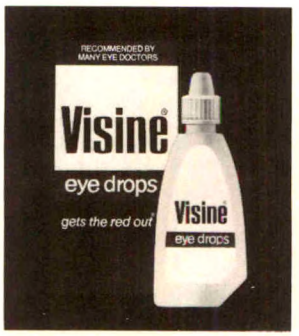

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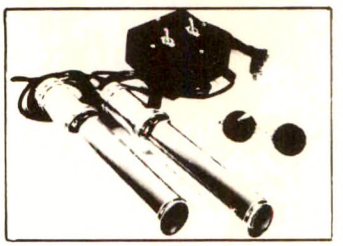

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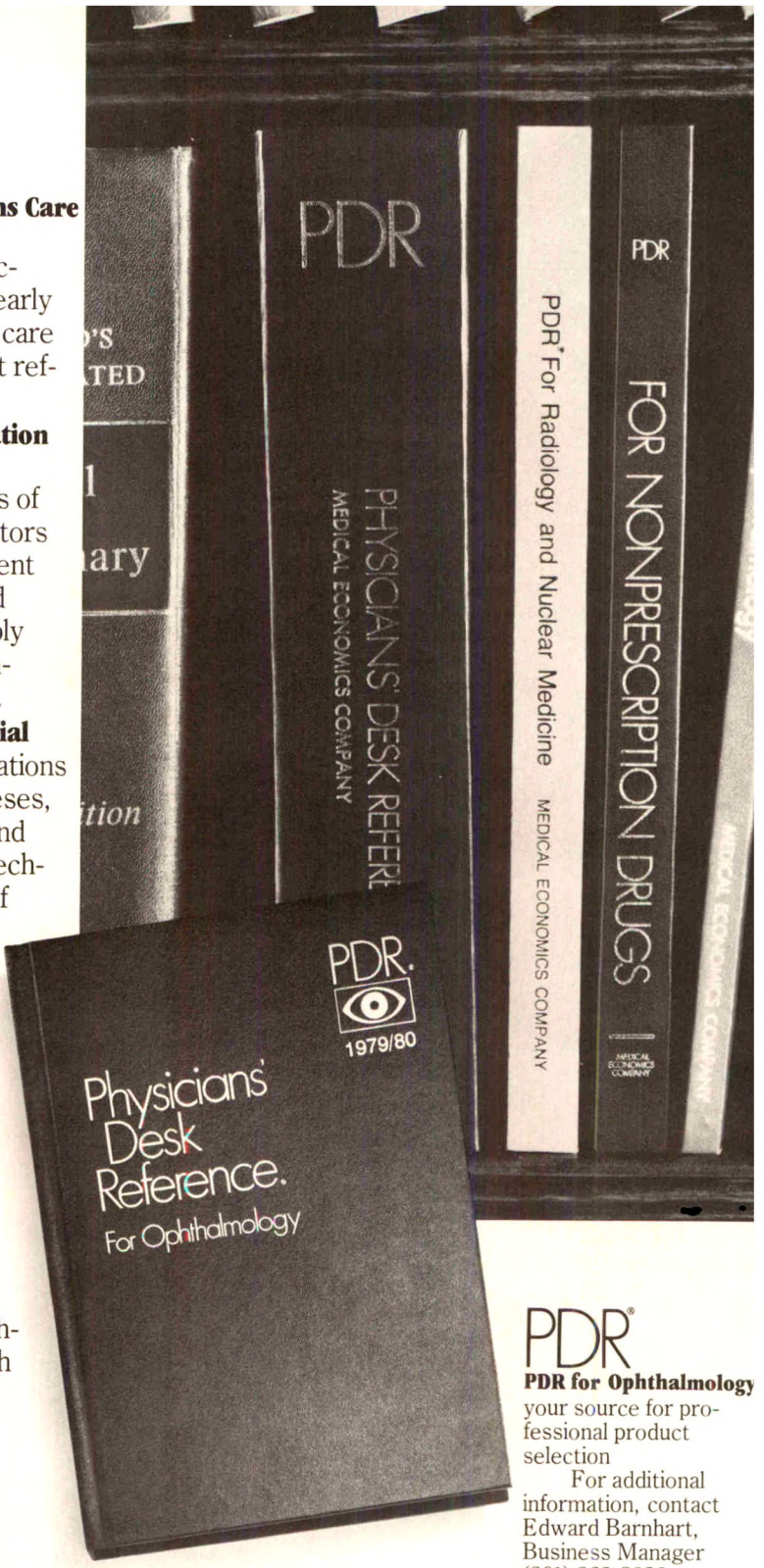

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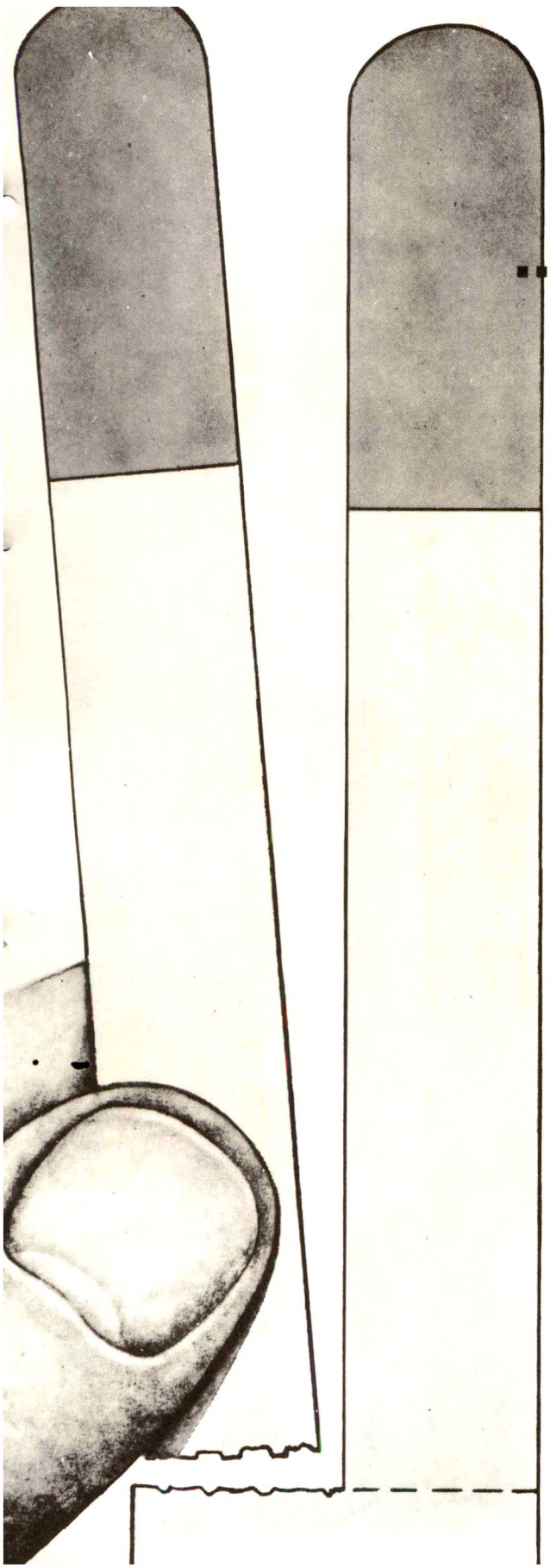

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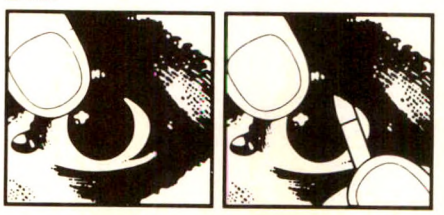

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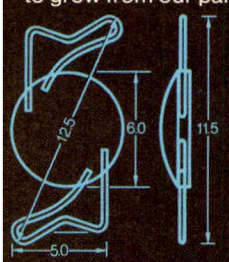
New IMPLENS 30—available only from McGhan—is the first of many developments to grow from our partnership with 3M and the surgeon, a good example of innovative logic applied to the practical needs of physicians and patients. John H. Sheets, MD, will discuss ECCE and demonstrate his implantation techniques using the new IMPLENS 30 in a forthcoming series of training seminars. To find out more about these seminars and about the new IMPLENS 30, please return the coupon.



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I would like the following:

- ☐ Information about the ½-day seminar in ECCE and implantation techniques by John H. Sheets, MD
- ☐ More information on the new IMPLENS 30
- ☐ One practice IMPLENS 30 lens

AJO-6

*Patent applied for.
Caution: Investigational device. Limited by Federal (U.S.A.) law to investigational use.

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Bleph-10
(sulfacetamide sodium)

BLEPH®-10 (sulfacetamide sodium) Liquifilm® sterile ophthalmic solution – CONTAINS: sulfacetamide sodium . . . 10.0%, Liquifilm (polyvinyl alcohol) . . . 1.4% with thimerosal (0.005%). INDICATIONS: For the treatment of conjunctivitis, corneal ulcer and other superficial ocular infections from susceptible microorganisms. CONTRAINDICATIONS: Hypersensitivity to sulfonamide preparations. PRECAUTIONS: (1) The solutions are incompatible with silver preparations. (2) Nonsusceptible organisms, including fungi, may proliferate with the use of this preparation. (3) Sulfonamides are inactivated by the aminobenzoic acid present in purulent exudates.

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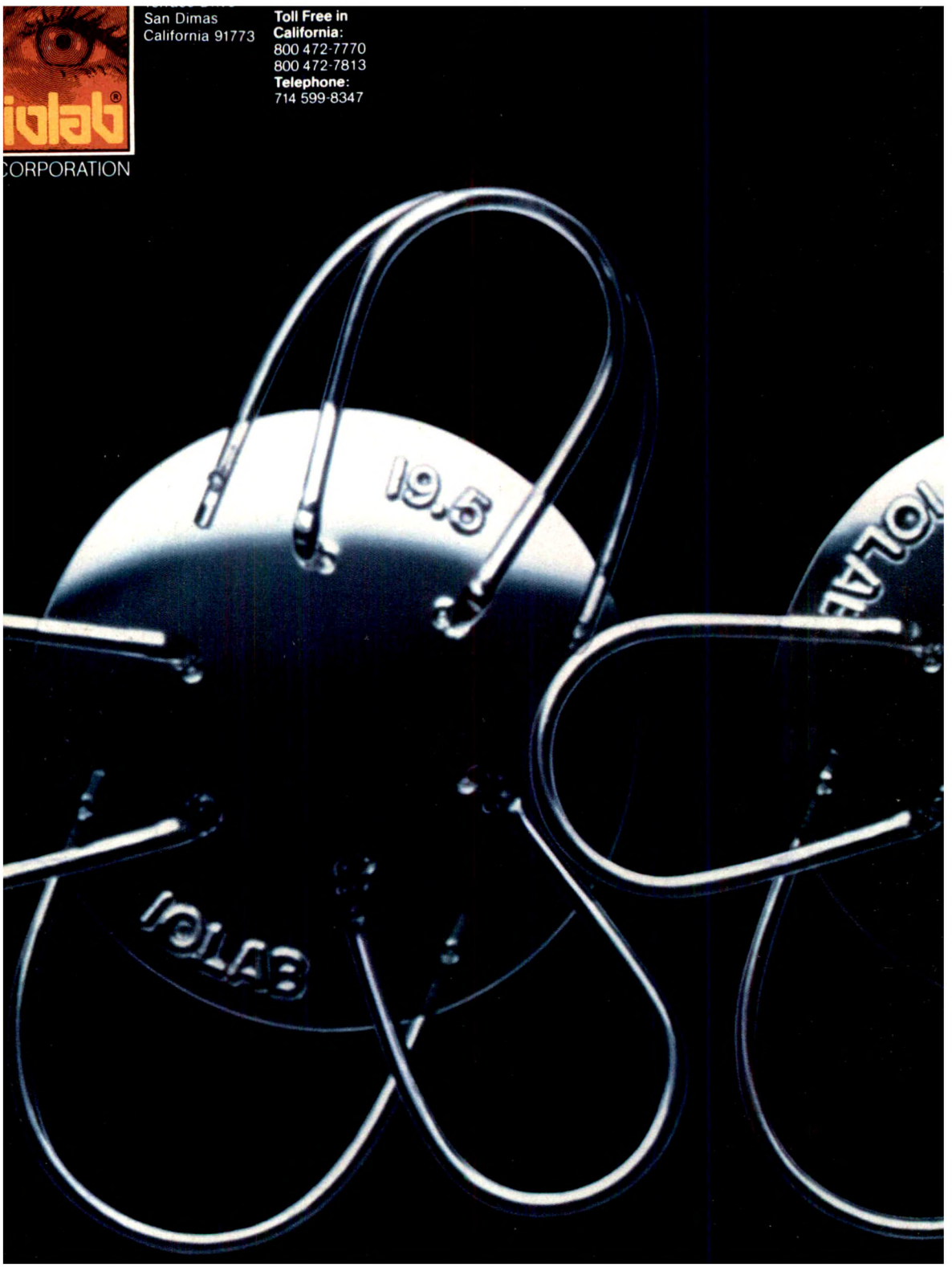

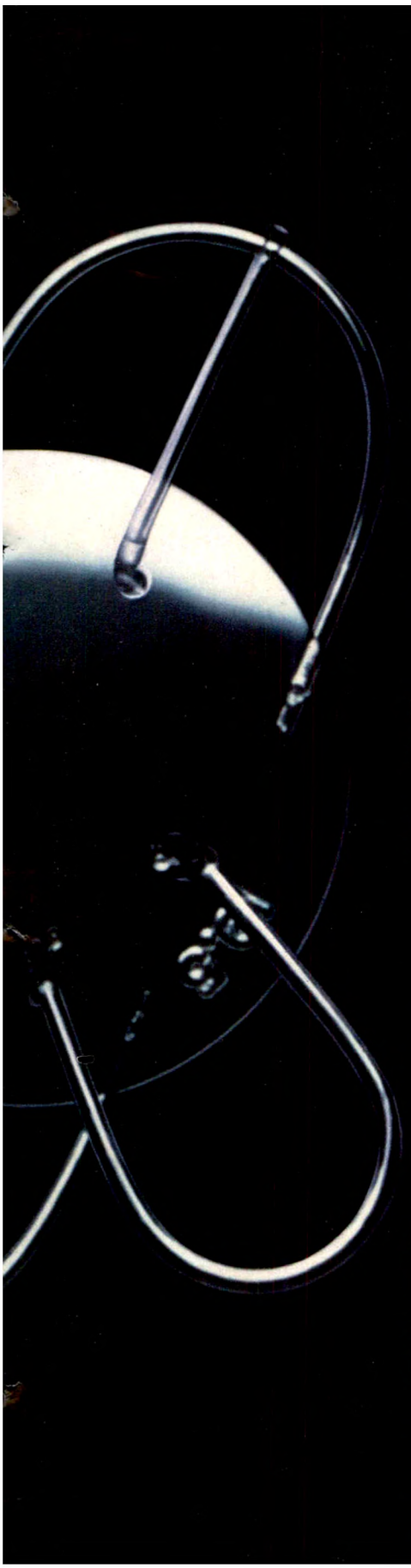

The Intracapsular Posterior Chamber Lens by IOLAB

iolab 103 S&K SEVERIN

This new lens combines intracapsular surgery with posterior chamber positioning, providing a practical alternative to prepupillary and anterior chamber lenses.

This lens possesses all or most of those attributes previously only associated with the IOLAB Model 101 Shearing™ Posterior Chamber Lens.

An artificial lens positioned in the posterior chamber most nearly duplicates the normal anatomical location in the eye.

The stability of the lens is provided by the haptics clasping both the anterior and posterior faces of the iris.

Additional Advantages:

- ☐ Easier insertion of the lens behind the iris
- ☐ Fixation at surgery so that the lens cannot move once it is in the posterior chamber
- ☐ Self-centering
- ☐ Suitable for intracapsular or extracapsular surgery

The Lens:

A plano convex disc 4.8mm in diameter; two posterior loops on the same plane as the disc; two choices available on the anterior configuration:
Model 103S: 3 anterior loops equally spaced on a 2.3mm pupil diameter
Model 103K: substitutes a prolene stave (clip) at the 12 o'clock position
The diameter of the haptic of both models is 8.2mm.

Optical Advantages:

- ☐ The posterior chamber lens lies closest to the nodal point of the eye.
- ☐ Image magnification and aniseikonia are maximally reduced.
- ☐ Lens edge glare is eliminated.
- ☐ Glitter is minimized.
- ☐ Shimmer is reduced.

Video Tape Available:

A video tape demonstrating implantation of the IOLAB Model 103S and 103K Severin lens with intracapsular surgery is available on loan without charge from IOLAB Corporation.

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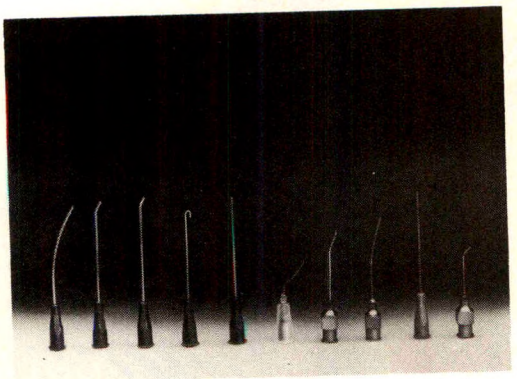
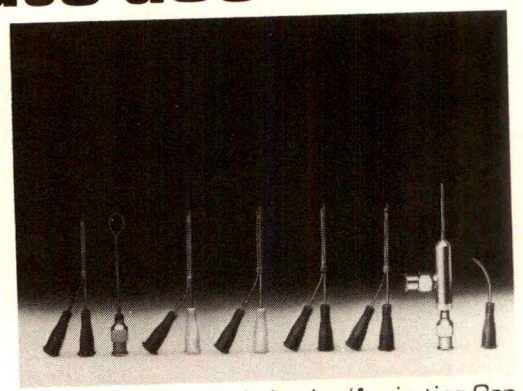


Left to right: Irrigating/Aspirating Cannula family—Curved, Posterior Capsule Polisher, Iris Retractor, U-shaped, Straight; Irrigating Cystotome, Anterior Chamber 16g, Lachrymal Cannula 26g, Retrobulbar 25g, Anterior Chamber 30g.



Left to right: Double Irrigating/Aspirating Cannula, Irrigating Vectis, 4 Double Irrigating/Aspirating Cannulae each with a different aperture location and size, Coaxial Irrigating/Aspirating Cannula, Single Aspirating Cannula.

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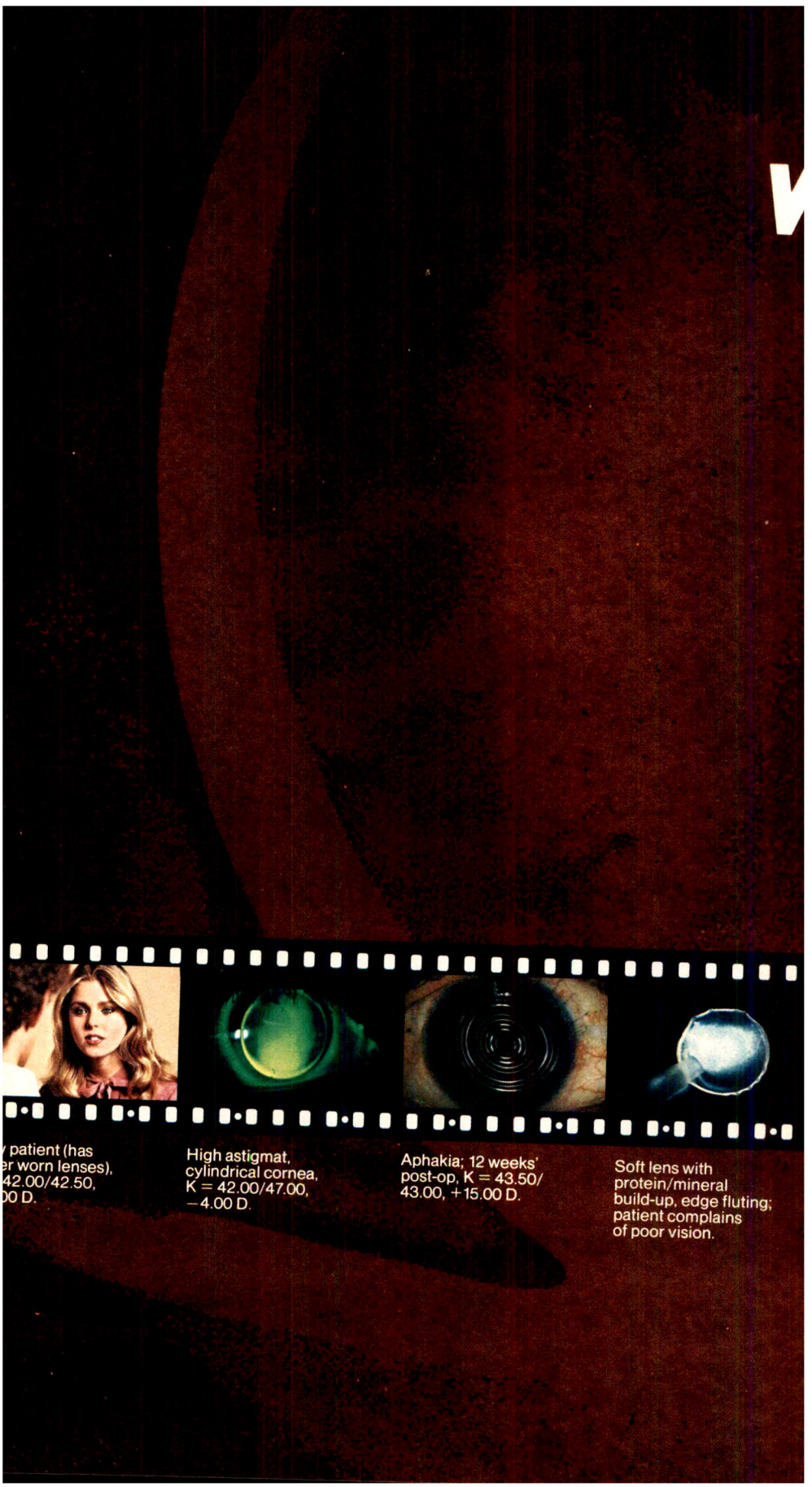
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Soft lens with
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build-up, edge fluting;
patient complains
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Now available in 8.5 & 9.5 mm diameters.

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On any patient needing a rigid lens.

Patients who have never worn lenses... patients who are tolerating compromised vision or annoying discomfort with their current lenses... highly astigmatic patients... aphakic patients... outright hard or soft lens failures... all are ideal candidates for POLYCON lenses.

POLYCON lenses add the important benefits of oxygen permeability to the desirable characteristics of PMMA lenses, to provide crisp, clear vision and avoid many of the problems associated with lens wear, particularly those due to corneal edema such as spectacle blur, limited hours of wear and discomfort.

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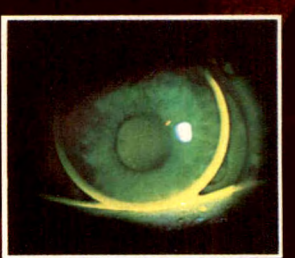
PMMA patient, complains of flare, glare and associated night vision problems.

PMMA patient for 4 years, complains of spectacle blur, discomfort; central corneal clouding.



POLYCON®

(silafocon A) CONTACT LENS

The clear choice in rigid lenses

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Brief Summary
(For full prescribing information, see package insert.)

INDICATIONS
The POLYCON contact lens is indicated for the correction of visual acuity for persons with nondiseased eyes having ametropias, including those with high degrees of corneal or refractive astigmatism, as well as aphakia.

CONTRAINDICATIONS
Acute and subacute inflammations of the anterior segment of the eye; any eye disease which affects the cornea or conjunctiva; insufficiency of lacrimal secretion; corneal hypoesthesia; or any systemic disease which may affect the eye or be exacerbated by wearing contact lenses.

WARNINGS
(1) If the lens becomes less comfortable to the wearer than when first placed on the wearer's cornea, a foreign body may be present. The patient should remove the lens immediately. If discomfort persists, an eye care practitioner should examine the patient as soon as possible to determine if any corneal abrasion, ulceration, irritation or infection is present.

(2) Aphakic patients should not be fitted during the postoperative period until the surgeon determines that the eye has healed completely.

(3) Only use Preflex® Sterile Cleaning Solution, Flex-Care® Sterile Solution, and Adapettes® Sterile Lubricating Solution with the POLYCON lens. Store ONLY in Flex-Care® Sterile Solution. Patients must adhere to recommended daily lens care regimen. FAILURE TO DO SO MAY RESULT IN DEVELOPMENT OF SERIOUS OCULAR INFECTIONS.

(4) Wearers must not use any medicaments or ophthalmic solutions other than Adapettes® solution prior to inserting the lens or while the lens is on the eye.

(5) Remove before sleeping or in the presence of noxious and irritating vapors.

PRECAUTIONS
THE POLYCON CONTACT LENS MUST BE BOTH CLEANED AND DISINFECTED DAILY. ONE PROCEDURE DOES NOT REPLACE THE OTHER. To disinfect the lens, it is stored in fresh Flex-Care® solution for a minimum of four hours daily in the patient lens storage case. After removal of the lens from the storage case, rinse the lens thoroughly with Flex-Care® solution and apply Adapettes® lubricating solution to the lens surfaces as a wetting agent prior to inserting the lens in the eye.

ADVERSE REACTIONS
Rainbows or halos around objects or blurring of the vision. Excessive tearing, unusual eye secretions, and photophobia.

Preflex,® Flex-Care® and Adapettes® are trademarks of Burton, Parsons & Company, Inc.

1-80

References

1 Multi-clinic study of 418 patients, data on file, Syntex Ophthalmics, Inc.

2 Korb JE, Finnemore VM: Corneal edema with polymethylmethacrylate vs. gas-permeable rigid polymer contact lenses of identical design. To be published.

3 Williams CE: New design concepts for permeable rigid contact lenses. *JAOA* 50:331-336, 1979.

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CORNEAL ENDOTHELIAL CELL ESTIMATES
AT YOUR SLIT LAMP IN 15 SECONDS WITH THE

MOSAIC MATCHER™

Designed by John Karickhoff, M.D.
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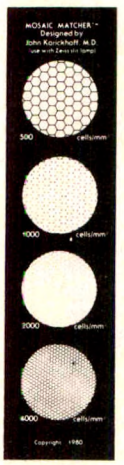

Just match the mosaic seen with the smallest (flare) beam of the slit lamp with the similar mosaic on the MOSAIC MATCHER.

- So simple, fast, inexpensive—use it routinely for **implant**, cataract, and corneal cases.
- Buy no reticle, attachments, specular microscope, camera, or film.
- No reticle to confuse the view during this and other examinations.
- No slit lamp modification or installation in the eyepiece.

Use with the following slit lamps: Zeiss 12.5x eyepiece, Haag-Streit 25x eyepiece, Bausch & Lomb 15x eyepiece.

Specify your slit lamp manufacturer.

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This is a comprehensive course in the surgical techniques of KPE. Detailed instruction is given in patient selection, preoperative considerations, the "nine steps of KPE," and postoperative care. Intraocular lenses and their use with KPE are also discussed. Live surgery is observed with commentary by experienced KPE surgeons. Courses are limited to fifteen to assure personalized attention during practice surgery sessions.

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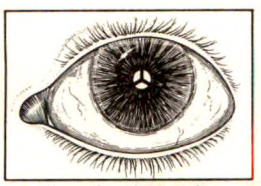
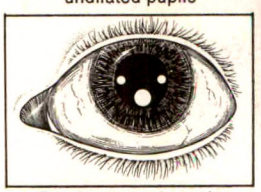
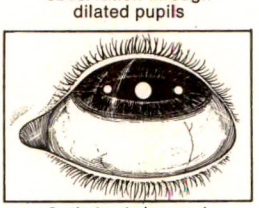


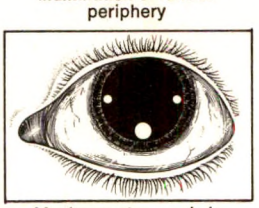
Binocular observation through small or undilated pupils



Routine posterior pole observation through dilated pupils



Optimized view and illumination of fundus periphery



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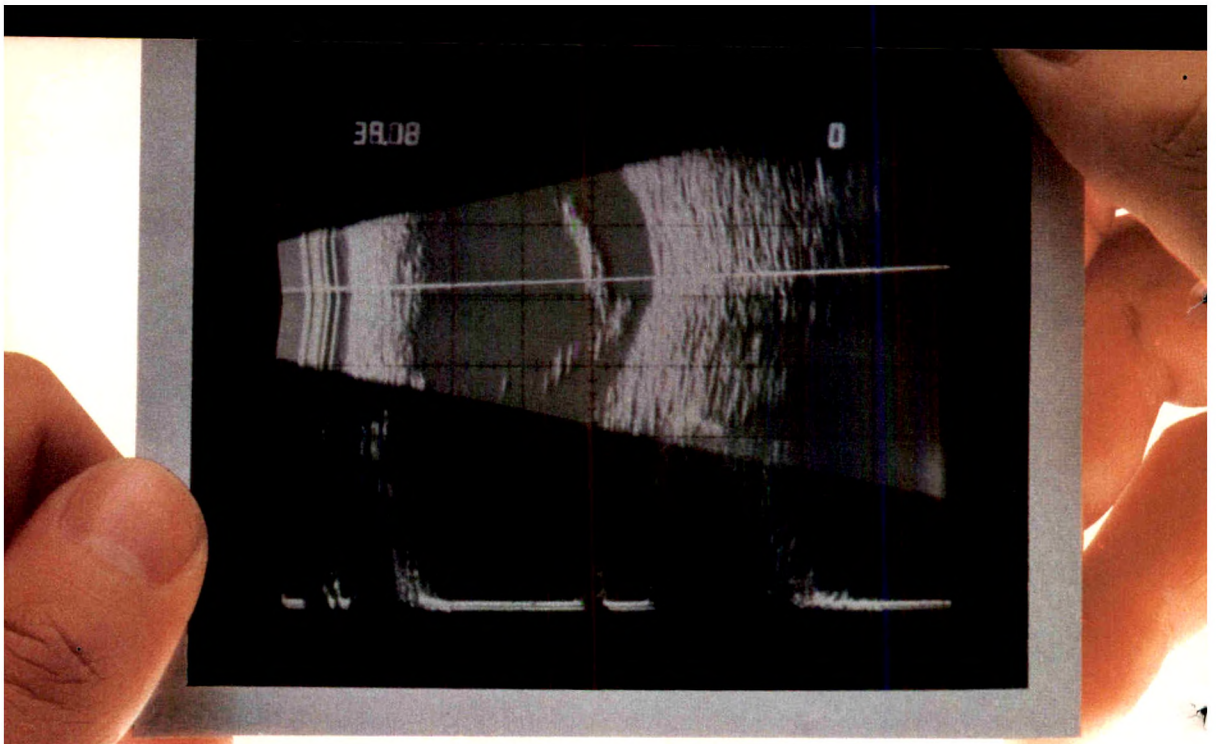

Typical funnel shaped retinal detachment converging at optic nerve head.

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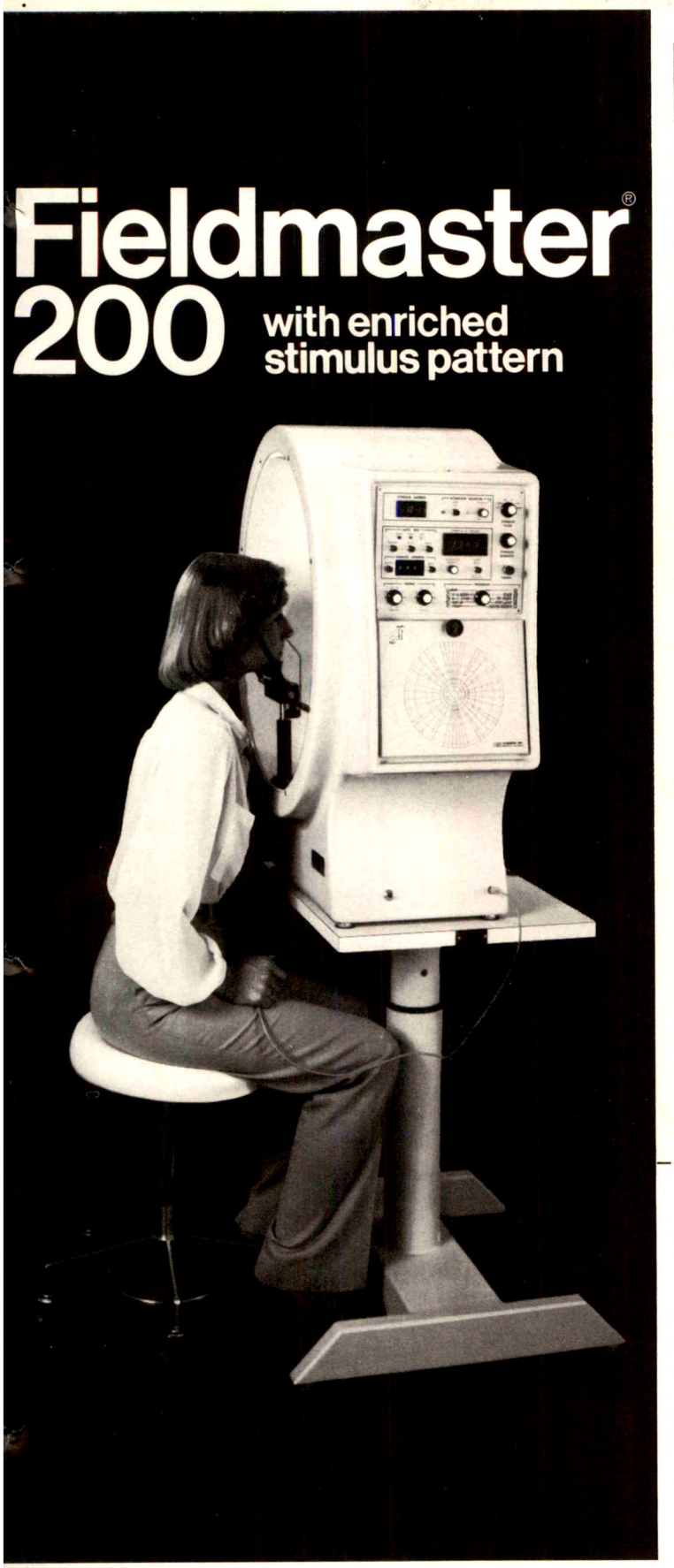

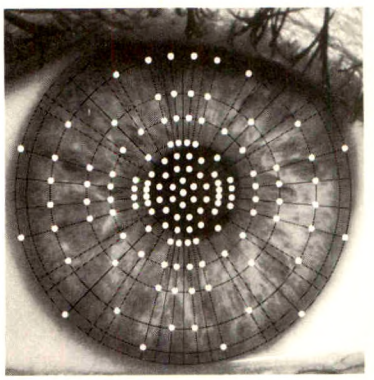

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Marked by itching or burning, hyperemia, lid edema and lacrimation or purulent discharge. Second only to refractive errors in frequency among ocular complaints.

*Bacterial corneal ulcer**
Pain, photophobia, lacrimation and blepharospasm are usual presenting symptoms. Prompt institution of therapy is vital to avoid possible visual difficulty.

* When due to susceptible microorganisms.

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Before prescribing, please consult complete product information, a summary of which follows:

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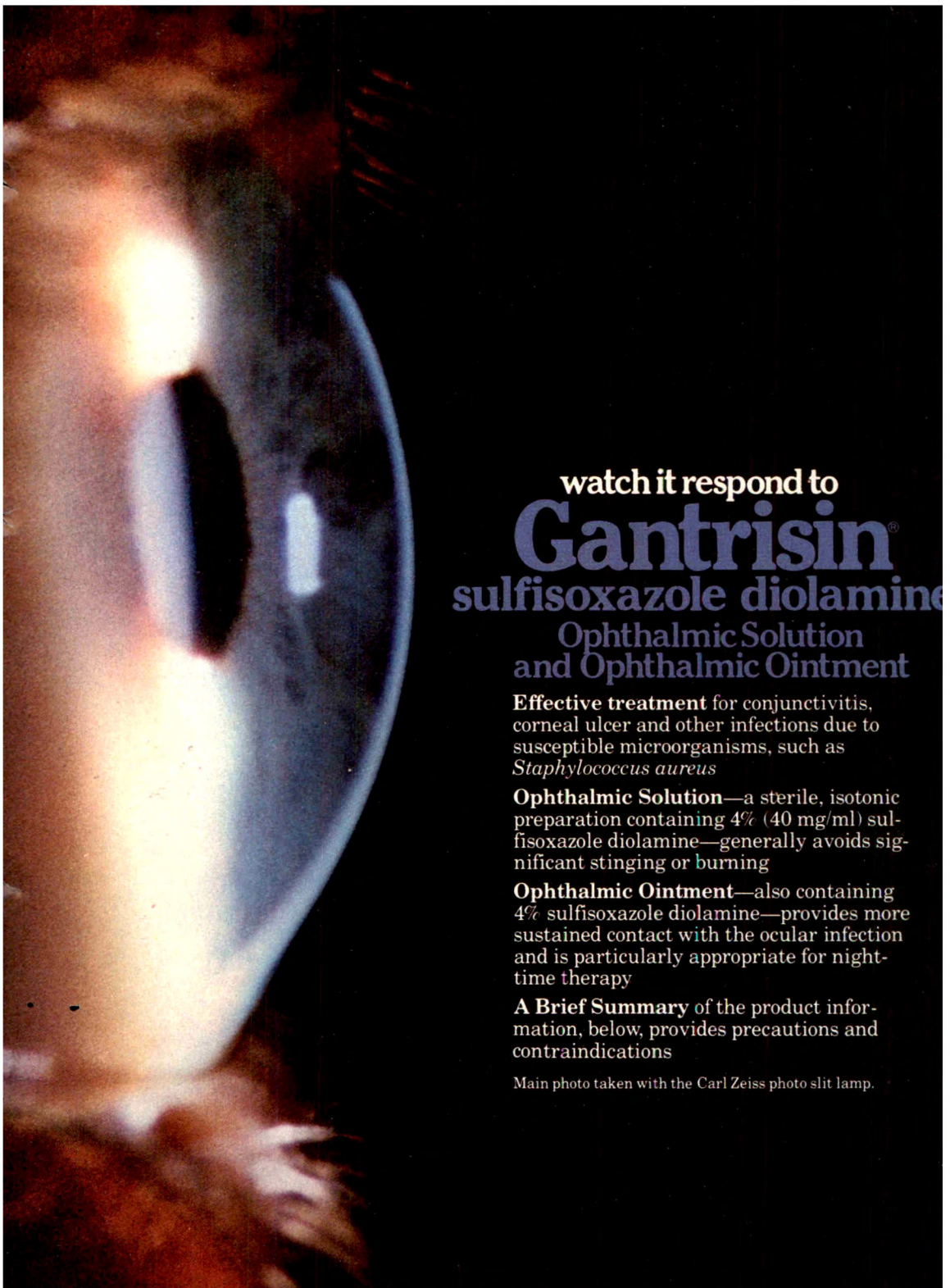
Contraindications: Hypersensitivity.
Precautions: Incompatible with silver preparations; inactivated by para-aminobenzoic acid in purulent exudates; may increase growth of nonsusceptible organisms, including fungi. Ointment may retard corneal healing. Discontinue use



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Effective treatment for conjunctivitis, corneal ulcer and other infections due to susceptible microorganisms, such as *Staphylococcus aureus*

Ophthalmic Solution—a sterile, isotonic preparation containing 4% (40 mg/ml) sulfisoxazole diolamine—generally avoids significant stinging or burning

Ophthalmic Ointment—also containing 4% sulfisoxazole diolamine—provides more sustained contact with the ocular infection and is particularly appropriate for nighttime therapy

A Brief Summary of the product information, below, provides precautions and contraindications

Main photo taken with the Carl Zeiss photo slit lamp.

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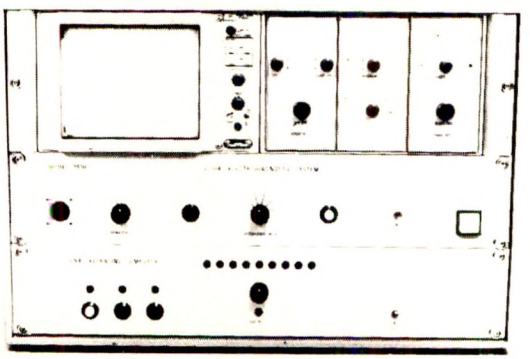

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Bright Flash Stimulator

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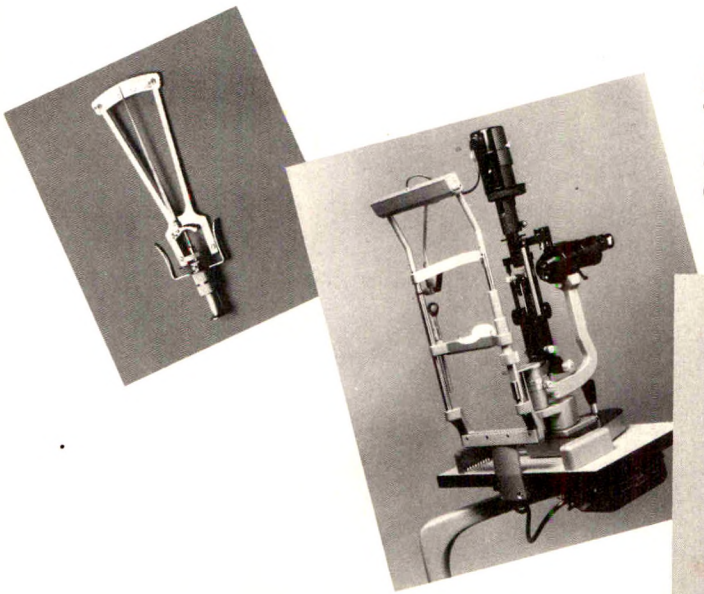

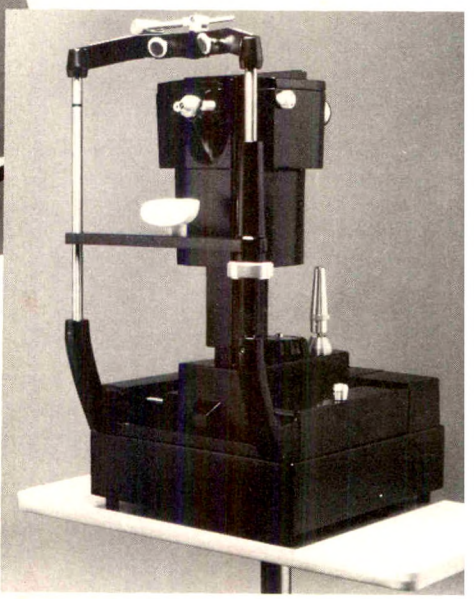

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1. Obstbaum,S.A. et al. Timolol: Effect on intraocular pressure in chronic open-angle glaucoma. Ann Ophthalmol 10(10): 1347-1351, 1978
2. A study conducted by an independent research organization. Allergan Pharmaceuticals Report Series #148, 1979.

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RISK FACTORS FOR GENETIC TYPING AND DETECTION IN RETINITIS PIGMENTOSA

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Some patients with retinitis pigmentosa can be genetically typed by family history into autosomal dominant, autosomal recessive, and X-chromosome-linked forms.[1-5] A large percentage of affected patients appear to be isolate cases with no family history of disease.[5-8] Classification of a patient into a genetic type has often been hampered by the unavailability of relatives for an ocular examination. We reviewed routine ocular examinations of patients with retinitis pigmentosa to determine which findings favor classification of a patient into one or another genetic type. Additionally, we compared affected patients with their normal relatives to determine which findings in a routine ocular examination help to identify relatives at higher risk for having the early stages of retinitis pigmentosa.

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MATERIAL AND METHODS

Data were collected from an outpatient population of patients with retinitis pigmentosa and their normal relatives from 1970 to 1979. Patients were referred from the outpatient facilities of the Massachusetts Eye and Ear Infirmary or from private ophthalmologists. In some instances the relatives of affected patients volunteered themselves when they learned they had an affected relative. All patients included in these analyses were examined by one of us (E.L.B.) and at least one other ophthalmologist.

Patients considered for this analysis were those who could be classified into one of the following groups: (1) autosomal dominant; (2) autosomal recessive; (3) X-chromosome-linked; (4) isolates; and (5) normal relatives. Patients were typed as autosomal dominant if their families showed evidence of transmission of the disease over three consecutive generations in at least one branch with or without evidence of reduced penetrance in other branches. Male patients were classified as autosomal recessive if they had at least one comparably affected female sibling. Female patients were typed as autosomal recessive if they had at least one sibling of either sex comparably affected. Cases of autosomal recessive disease required that parents of affected patients be normal. Male patients were

classified in the X-chromosome-linked group only if they had no female relatives who were comparably affected at the same age, if at least the mother or one daughter of an affected male in the family showed the carrier state as determined by a peripheral patch of bone spicule pigmentation, a tapetal-like reflex in the macula, or an abnormal electroretinogram (ERG),[9] and if no father-to-son transmission was observed. Patients with retinitis pigmentosa were classified as isolates if no relatives were affected and if no family history of retinitis pigmentosa could be elicited. All affected patients had either nondetectable full-field ERGs or full-field ERGs that were reduced in amplitude and delayed in cone or rod, or both, b-wave implicit time.[10] Relatives of this affected population at risk for inheriting retinitis pigmentosa were classified as normal if they had normal fundi and normal full-field ERGs, because such relatives would not be expected to develop retinitis pigmentosa at a later time.[10] The typing of families was achieved in the following way: (a) obtaining a detailed family history from all affected patients, (b) examining first-degree relatives of affected patients in most cases, and (c) securing records of examinations of affected relatives from other ophthalmologists in a few cases. We excluded patients with severe deafness, aphakia, or any evidence of systemic abnormalities known to be associated with retinitis pigmentosa, patients with a vague family history, and families with more than one affected male and no affected female relatives in which the mode of inheritance was unclear. We also excluded patients with sector retinitis pigmentosa who had reduced ERG amplitudes but normal cone and rod b-wave implicit times.[10]

Data were collected from this outpatient population with respect to best corrected Snellen visual acuity in each eye, cycloplegic refraction as determined with retinoscopy after 10% phenylephrine HCl and 1% cyclopentolate HCl, appearance of the lens on slit-lamp examination, and appearance of the fundus with respect to the presence or absence of bone spicule pigmentation. For patients with astigmatism, the refractive error was coded in the minus cylinder form. Attention was given to the patient's history with respect to presence or absence of parental consanguinity and age of onset of night blindness.

The data based on the ocular examinations were coded by one person and checked by another; data were then keypunched, verified, and stored on a magnetic tape for data processing. All data were then validated for errors and inconsistencies and corrected appropriately. The data were computer analyzed.

From our population two files were constructed. File A contained one randomly selected affected patient from each family. For File B one affected patient was randomly selected (if present) from each family for each of the following age groups: 6 to 19 years, 20 to 39 years, and 40 years and older. File A alone was used for analysis of the family history of presence or absence of consanguinity and for the analysis of age of onset of night blindness. File B alone was used for analysis of visual acuity and presence or absence of cataracts or bone spicule pigmentation. Both Files A and B were used for analysis of spherical and cylindrical refractive errors.

Data for such variables as best corrected visual acuity, spherical refractive error, and the like, were analyzed with standard contingency table methods,[11] including the Yates-corrected chi-square test for 2×2 tables, and Fisher's exact test when any expected value in a 2×2 table was less than 5. The age of onset of night blindness by history was evaluated with the life table method of analysis.[12]

Analyses were also done within given families in File A to compare each autosomal dominant, autosomal recessive, X-chromosome-linked, or isolate patient to all of his or her normal relatives within 15 years of age in our files. The normal relatives included in these analyses (male relatives in the case of X-chromosome-linked disease) were at risk for having retinitis pigmentosa, but had normal fundi and normal full-field ERGs. The Mantel-Haenszel test combining evidence from several 2 × 2 tables[13] was used to compare affected patients to their normal relatives; specifically, the observed number of affected patients with a particular characteristic on an ocular examination was compared with the expected number of such patients with that characteristic over the 35 families available for these analyses. The mean age for affected patients included in this analysis was 25.5 ± 1.8 years (mean ± S.E.M.) and for normal relatives was 22.3 ± 1.4 years (not significant by Student's *t*-test); and the proportion of males was 57% among affected patients and 60% among normal relatives (not significant by chi-square test). Analyses were done on those variables (best corrected visual acuity in the better eye and cylindrical refractive error in the less astigmatic eye) that were found (see Results section) not to differ substantially among the different groups of affected patients. For these analyses, families from the autosomal dominant, autosomal recessive, X-chromosome-linked, and isolate groups were considered as a single population. These comparisons were also performed within the four groups but not enough families with normal relatives were available within each group to achieve sufficient statistical power.

Results

Table 1 provides demographic data on our study populations of patients with retinitis pigmentosa. One study population (File A) consisted of one randomly selected affected patient from each of 456 families; 310 (68%) of these families were from New England and New York, 19 (26%) were from the rest of the United States, and 27 (6%) were from foreign countries. Among these families, 46 (10.1%) were autosomal dominant, 64 (14%) were autosomal recessive, 27 (5.9%) were X-chromosome-linked, and 319 (70%) were isolates. A slight female preponderance was observed in the autosomal recessive group in that patients in this group came from families that included at least one affected female. A preponderance of younger patients was noted in the X-chromosome-linked group, possibly because of the severity of the disease. A second study population (File B) consisted of one randomly selected affected patient per family (if present) from each of three age groups. The demographic characteristics of File B were similar to those of File A with respect to age, sex, and geographic distribution. The percentages of dominant and X-chromosome-linked cases were larger in File B than in File A.

Table 2, based on File B, shows that patients with X-chromosome-linked retinitis pigmentosa had a visual acuity of 6/15 (20/50) or less in the better eye in the age group 20 to 39 years significantly more often than the dominant and isolate groups. For this criterion, the dominant group in the 6- to 19-year age range tended to have a visual acuity of 6/12 (20/40) or better in at least one eye more often than the other groups, but this tendency was not statistically significant.

Table 3, based on File A, shows the spherical refractive error in the less myopic eye in patients with retinitis pigmentosa over all age groups. Intergroup comparisons were performed for four levels of myopia from -1.0 to -4.0 diopters and showed that the X-

TABLE 1

AGE-SEX DISTRIBUTION OF STUDY POPULATION WITH RETINITIS PIGMENTOSA*

Type	6-19 yrs	20-39 yrs	40+ yrs	Total (%)	Male	Female
FILE A—BASED ON RANDOM SELECTION OF ONE AFFECTED PERSON FROM EACH FAMILY						
DOM	8	18	20	46	24	22
(%)	(17.4)	(39.1)	(43.5)	(10.1)	(52.2)	(47.8)
AR	18	20	26	64	25	39
(%)	(28.1)	(31.3)	(40.6)	(14.0)	(39.1)	(60.9)
XL	8	18	1	27	27	0
(%)	(29.6)	(66.7)	(3.7)	(5.9)	(100.0)	(0.0)
ISO	50	150	119	319	183	136
(%)	(15.7)	(47.0)	(37.3)	(70.0)	(57.4)	(42.6)
Total affected	84	206	166	456	259	197
(%)	(18.4)	(45.2)	(36.4)	(100.0)	(56.8)	(43.2)
FILE B—BASED ON RANDOM SELECTION OF ONE AFFECTED PERSON FROM EACH AGE GROUP (IF PRESENT) FROM EACH FAMILY						
DOM	18	28	23	69	36	33
(%)	(26.1)	(40.6)	(33.3)	(14.1)	(52.2)	(47.8)
AR	19	21	27	67	26	41
(%)	(28.4)	(31.3)	(40.3)	(13.7)	(38.8)	(61.2)
XL	13	19	2	34	34	0
(%)	(38.2)	(55.9)	(5.9)	(7.0)	(100.0)	(0.0)
ISO	50	150	119	319	183	136
(%)	(15.7)	(47.0)	(37.3)	(65.2)	(57.4)	(42.6)
Total affected	100	218	171	489	279	210
(%)	(20.5)	(44.6)	(35.0)	(100.0)	(57.1)	(42.9)

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate.

TABLE 2

VISUAL ACUITY IN PATIENTS WITH RETINITIS PIGMENTOSA*

	+†	−†	Total	%+	DOM	AR	XL	ISO
	Ages 6-19 yrs				Intergroup Comparisons‡			
DOM	2	16	18	11.1	N/A	NS	NS	NS
AR	8	11	19	42.1	NS	N/A	NS	NS
XL	6	7	13	46.2	NS	NS	N/A	NS
ISO	18	32	50	36.0	NS	NS	NS	N/A
	Ages 20-39 yrs				Intergroup Comparisons‡			
DOM	7	21	28	25.0	N/A	NS	.003	NS
AR	9	12	21	42.9	NS	N/A	NS	NS
XL	14	5	19	73.7	.003	NS	N/A	.008
ISO	57	91	148	38.5	NS	NS	.008	N/A
	Ages 40+ yrs				Intergroup Comparisons‡			
DOM	11	12	23	47.8	N/A	NS	N/A	NS
AR	13	14	27	48.1	NS	N/A	N/A	NS
XL	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ISO	54	64	118	45.8	NS	NS	N/A	N/A

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate; N/A, not applicable; NS, not significant ($P > .05$).

†+ indicates visual acuity of 6/15 (20/50) or less in the better eye; −, 6/12 (20/40) or better in the better eye.

‡For most comparisons, P values were based on a chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5.

TABLE 3

REFRACTIVE ERROR (SPHERE) IN THE LESS MYOPIC EYE* IN PATIENTS WITH RETINITIS PIGMENTOSA OVER ALL AGE GROUPS†

					DOM	AR	XL	ISO
		Group A (≤−1)			Intergroup Comparisons§			
	≤−1	>−1‡	Total	%≤−1				
DOM	6	34	40	15.0	N/A	NS	<.001	.003
AR	21	41	62	33.9	NS	N/A	.001	NS
XL	20	7	27	74.1	<.001	.001	N/A	<.001
ISO	101	205	306	33.0	.033	NS	<.001	N/A
		Group B(≤−2)			Intergroup Comparisons§			
	≤−2	>−2‡	Total	%≤−2				
DOM	4	36	40	10.0	N/A	NS	<.001	NS
AR	12	50	62	19.4	NS	N/A	<.001	NS
XL	18	9	27	66.7	<.001	<.001	N/A	<.001
ISO	73	233	306	23.9	NS	NS	<.001	N/A
		Group C (≤−3)			Intergroup Comparisons§			
	≤−3	>−3‡	Total	%≤−3				
DOM	4	36	40	10.0	N/A	NS	<.001	NS
AR	10	52	62	16.1	NS	N/A	<.001	NS
XL	16	11	27	59.3	<.001	<.001	N/A	<.001
ISO	50	256	306	16.3	NS	NS	<.001	N/A
		Group D(≤−4)			Intergroup Comparisons§			
	≤−4	>−4‡	Total	%≤−4				
DOM	1	39	40	2.5	N/A	NS	<.001	NS
AR	5	57	62	8.1	NS	N/A	<.001	NS
XL	16	11	27	59.3	<.001	<.001	N/A	<.001
ISO	35	271	306	11.4	NS	NS	<.001	N/A

*As determined by spherical refraction and not spherical equivalent.

†DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate; N/A, not applicable; NS, not significant (P>.05).

‡Includes hyperopic, plano, and myopic refractive errors up to but not inclusive of −1.0 diopter (Group A), −-2.0 diopters (Group B), −3.0 diopters (Group C), and −4.0 diopters (Group D).

§For most comparisons, P values were based on a chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5.

chromosome-linked group differed significantly from other affected groups for any level of myopia tested. For example, patients with known X-chromosome-linked disease were 2.8 to 6.7 times more likely to have 2.0 or more diopters of myopia than any of the other affected groups. The isolate group differed significantly from the dominant group for the criterion of 1.0 or more diopters of myopia in the less myopic eye. The same analysis was done for spherical equivalent (sphere + 0.5 cylindric power) and similar conclusions were reached as with spherical refraction alone. These analyses were repeated on data from File B within specific age groups, and observations were comparable to those reported in Table 3. Table 4, based on File A, shows the cylindrical refractive error in the eye with less astigmatism in patients with retinitis pigmentosa over all age groups. No significant differences were observed among the groups with respect to the power of the cylindrical refractive error. With respect to the axis of minus

TABLE 4

REFRACTIVE ERROR (CYLINDER) IN THE EYE WITH LESS ASTIGMATISM IN PATIENTS WITH RETINITIS PIGMENTOSA OVER ALL AGE GROUPS*

					DOM	AR	XL	ISO
	Group A (≥1.0 Diopter)				Intergroup Comparisons†			
	≥1.0	<1.0	Total	%≥1.0				
DOM	16	26	42	38.1	N/A	NS	NS	NS
AR	27	35	62	43.5	NS	N/A	NS	NS
XL	17	10	27	63.0	NS	NS	N/A	NS
ISO	151	155	306	49.3	NS	NS	NS	N/A
	Group B (≥2.0 Diopters)				Intergroup Comparisons†			
	≥2.0	<2.0	Total	%≥2.0				
DOM	6	36	42	14.3	N/A	NS	NS	NS
AR	10	52	62	16.1	NS	N/A	NS	NS
XL	7	20	27	25.9	NS	NS	N/A	NS
ISO	51	255	306	16.7	NS	NS	NS	N/A

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate; N/A, not applicable; NS, not significant ($P > .05$).

†For most comparisons, P values were based on a chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5.

cylinder (Table 5) for patients with ≥ 1.0 diopter of astigmatism in both eyes, the X-chromosome-linked group had a vertical or oblique axis (that is, 31 to 149 degrees) in one or both eyes significantly more often than the other affected groups. These analyses were repeated within specific age groups (File B) with similar results.

The prevalence of posterior subcapsular cataracts in both eyes, based on File B, increased with age for all groups (Table 6). In most instances there were no substantial differences in the age-specific prevalences among the different groups; the one exception was the significantly greater prevalence of cataracts in the X-chromosome-linked group as com-

TABLE 5

AXIS OF CYLINDER* IN PATIENTS WITH RETINITIS PIGMENTOSA OVER ALL AGES†

	+‡	−‡	Total	% +	DOM	AR	XL	ISO
	Patients				Intergroup Comparisons§			
DOM	1	14	15	6.7	N/A	NS	.003	NS
AR	6	21	27	22.2	NS	N/A	.012	NS
XL	11	6	17	64.7	.003	.012	N/A	.004
ISO	41	110	151	27.2	NS	NS	.004	N/A

*Includes only those patients with astigmatism ≥1.0 diopter in both eyes. Refractive error was coded in minus cylinder form for this analysis.

†DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate; N/A, not applicable; NS, not significant ($P > .05$).

‡+ indicates vertical or oblique in either eye (vertical or oblique = 31-149°); −, horizontal in both eyes (horizontal = 0-30°, 150-180°).

§For most comparisons, P values were based on chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5.

TABLE 6

PREVALENCE OF CATARACTS IN PATIENTS WITH RETINITIS PIGMENTOSA*

	+†	−†	Total	% +	DOM	AR	XL	ISO
	Ages 6-19 yrs				Intergroup Comparisons‡			
DOM	0	17	17	0.0	N/A	NS	NS	NS
AR	1	17	18	5.6	NS	N/A	NS	NS
XL	0	13	13	0.0	NS	NS	N/A	NS
ISO	6	40	46	13.0	NS	NS	NS	N/A
	Ages 20-39 yrs				Intergroup Comparisons‡			
DOM	13	12	25	52.0	N/A	NS	NS	NS
AR	7	11	18	38.9	NS	N/A	NS	NS
XL	13	5	18	72.2	NS	NS	N/A	.012
ISO	55	89	144	38.2	NS	NS	.012	N/A
	Ages 40+ yrs				Intergroup Comparisons‡			
DOM	17	5	22	77.3	N/A	NS	N/A	NS
AR	15	11	26	57.7	NS	N/A	N/A	NS
XL	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ISO	59	47	106	55.7	NS	NS	N/A	NS

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate; N/A, not applicable; NS, not significant ($P > .05$).

†+ indicates posterior subcapsular cataracts in both eyes; −, absence of posterior subcapsular cataracts in one or both eyes.

‡For most comparisons, P values were based on a chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5.

pared to the isolates in the 20- to 39-year age group.

Bone spicule pigmentation in all four quadrants of the midperipheral fundus of both eyes was seen in most patients (File B) between the ages of 6 and 19 years in the autosomal recessive, X-chromosome-linked, and isolate groups, but was seen in the minority of cases with dominant disease (Table 7). The dominant group had a significantly smaller percentage of patients with bone spicule pigmentation in all four quadrants of both eyes than the X-chromosome-linked and isolate groups. Additionally, the autosomal recessive group had a significantly smaller percentage of patients with respect to this risk factor than the

TABLE 7

BONE SPICULE PIGMENTATION IN PATIENTS WITH RETINITIS PIGMENTOSA*

	+†	−†	Total	% +	DOM	AR	XL	ISO
	Ages 6-19 yrs				Intergroup Comparisons‡			
DOM	6	11	17	35.3	N/A	NS	.002	.032
AR	9	6	15	60.0	NS	N/A	.044	NS
XL	12	0	12	100.0	.002	.044	N/A	NS
ISO	28	12	40	70.0	.032	NS	NS	N/A

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate; N/A, not applicable; NS, not significant ($P > .05$).

†+ indicates present in all four quadrants in both eyes; −, absent in all four quadrants in both eyes.

‡For most comparisons, P values were based on a chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5.

TABLE 8

HISTORY OF CONSANGUINITY IN PARENTS OF PATIENTS WITH RETINITIS PIGMENTOSA OVER ALL AGE GROUPS*

	+†	−†	Total	% +	DOM	AR	XL	ISO
		Patients			Intergroup Comparisons‡			
DOM	1	38	39	2.6	N/A	.031	NS	NS
AR	11	45	56	19.6	.031	N/A	.047	NS
XL	0	24	24	0.0	NS	.047	N/A	NS
ISO	38	258	296	12.8	NS	NS	NS	N/A

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate.
†+ indicates presence of consanguinity; −, absence of consanguinity.
‡For most comparisons, P values were based on a chi-square test comparing the subgroups in the corresponding rows and columns. P values were based on Fisher's exact test when any expected value in the corresponding 2 × 2 table was less than 5. N/A = not applicable; NS = not significant (P > .05).

X-chromosome-linked group. Similar analyses performed on patients in the age groups 20 to 39 years and 40 years or older showed no significant differences among affected groups.

A history of consanguinity was more prevalent in parents of patients in the autosomal recessive group than in the dominant or X-chromosome linked groups (Table 8). Intergroup comparisons, based on File A, showed that these differences were significant. A life table analysis (Table 9) for age of onset of night blindness by history, based on File A, showed that the age of onset of night blindness was not the same in the four groups of affected patients (P = .004). In particular, the onset of the symptom of

TABLE 9

AGE OF ONSET OF NIGHT BLINDNESS BY HISTORY IN PATIENTS WITH RETINITIS PIGMENTOSA*

	N‡	Probability of Being Night-blind by Age 10, 20, 30, or 40 yrs†			
		10	20	30	40
DOM	41	.415	.745	.893	.964
AR	53	.396	.613	.735	.866
XL	23	.565	.870	1.000	1.000
ISO	257	.335	.636	.792	.878

Comparison§ of Observed (O) and Expected (E) Numbers of Patients Becoming Night Blind as Computed from a Life Table Analysis

	Observed	Expected
DOM	38.0	28.8
AR	49.0	53.7
XL	23.0	12.3
ISO	242.0	257.2

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate.
†As estimated from life tables.
‡Refers to number of cases with available history to include in the life table analysis.

§$\chi^2_3 = \sum_{i=1}^{4} (O_i - E_i)^2/E_i = 13.4$, P = .004.

night blindness occurred early more often in patients with dominant and X-chromosome-linked disease than in the other affected groups.

Table 10, based on the comparison of affected patients to their normal relatives within families, shows that normal relatives in the autosomal dominant, autosomal recessive, X-chromosome-linked, and isolate groups, taken as one population, differ significantly from their affected relatives (a subgroup of File A) with respect to best corrected visual acuity in the better eye. This was true not only for the criterion of visual acuity of 6/15 (20/50) or worse, but also for visual acuity of 6/9 (20/30) or worse in the better eye. Normal relatives also differed significantly from their affected relatives with respect to cylindrical refractive error; specifically, affected patients showed a cylindrical refractive error of 1.0 or more diopters in the less astigmatic eye significantly more often than their normal relatives. Similar trends were observed when these data were analyzed for families in the autosomal dominant, autosomal recessive, X-chromosome-linked, and isolate groups, respectively; but the numbers of families in each group were too small to achieve sufficient statistical power.

Discussion

Certain findings in a routine ocular examination are significantly more prevalent in different types of retinitis pigmentosa (Table 11). For example, factors favoring X-chromosome-linked disease in affected male patients include visual acuity reduced to 6/15 (20/50) or worse in the better eye between ages 20 and 39 years, a spherical refractive error of two or more diopters of myopia in the less myopic eye, presence of a vertical or oblique axis of cylinder in at least one eye among patients with astigmatism of ≥ 1.0 diopter in both eyes, and the onset of the symptom of night blindness by age 20 years. Male patients who have these risk factors should be strongly encouraged to have female relatives examined and tested with the ERG to see if they have the carrier state of X-chromosome-linked disease.[9] Male patients without these findings and an unremarkable family history are more likely to be in the autosomal recessive or isolate groups.

Table 11 also summarizes risk factors favoring dominant disease; these include lack of bone spicule pigmentation in all four quadrants of both eyes up to age 19 years and onset of the symptom of night blindness by age 20 years. Patients with dominant disease tend to have a spherical refractive error that is hyperopic, plano, or slightly myopic (that is, up to but not inclusive of -1.0 diopter) in contrast to the one or more diopters of myopia usually seen in X-chromosome-linked disease (Table 3). Patients with these risk factors, regardless of family history, should be encouraged to have other relatives examined. Retinitis pigmentosa can be transmitted by a dominant mode with reduced penetrance and patients can have dominantly inherited disease even if both parents have no symptoms or signs of retinitis pigmentosa.[14-16]

In a previous study François and Verriest[5] correlated the type of inheritance with the spherical refractive error and showed that myopia of more than 2.0 diopters was observed in 29% of 76 autosomal recessive cases, in all nine X-chromosome-linked cases, and 23% of 30 dominant cases. The difference between the prevalence of myopia in autosomal recessive and dominant groups was not significant, but the difference between the autosomal recessive and X-chromosome-linked groups was highly significant.[5] Our data are compatible with these findings in that the prevalence of 2 or more diopters of myopia in

TABLE 10

COMPARISON OF AFFECTED PATIENTS IN THE AUTOSOMAL DOMINANT, AUTOSOMAL RECESSIVE, X-CHROMOSOME-LINKED, AND ISOLATE GROUPS TO THEIR AGE-MATCHED NORMAL RELATIVES (BASED ON 35 AFFECTED AND 53 NORMAL RELATIVES FROM 35 FAMILIES)

Characteristic	Affected Patients with Characteristic (%)	Normal Relatives with Characteristic (%)	Observed* (O)	Expected† (E)	Variance (V)	$\chi^{2‡}$	P Value
Visual acuity 6/9 (20/30) or less in better eye	80.0	5.7	28.0	13.1	6.0	34.3	<.001
Visual acuity 6/15 (20/50) or less in better eye	42.9	1.9	15.0	6.7	3.2	19.0	<.001
Refractive error (cylinder) ≥1 in less astigmatic eye	48.5	11.8	16.0	9.5	4.5	7.9	.005

*Observed number of affected patients with characteristic.

†Expected number of affected patients with characteristic was calculated under the null hypothesis that affected patients and their normal relatives were equally at risk for having the stated characteristic in a given family.

‡Based on the Mantel-Haenszel test statistic, $S=(|O-E|-0.5)^2/V \sim \chi_1^2$ where O is the observed and E the expected number of affected patients with the characteristic and where

$E = \sum_{i=1}^{35} a_i/(N_i + 1)$, $V = \sum_{i=1}^{35} a_i (N_i + 1 - a_i)/(N_i + 1)^2$ and a_i = the total number of persons in the ith family with the characteristic, i . . . ,35 and N_i = the number of normal relatives in the ith family, i=1, . . . ,35.

TABLE 11

FINDINGS IN A ROUTINE OCULAR EXAMINATION OF AFFECTED PATIENTS THAT FAVOR DIFFERENT TYPES OF RETINITIS PIGMENTOSA*

Variable	Age Group (yrs)	DOM	AR	XL	ISO
Visual acuity 6/15 (20/50) or less in better eye	20-39	−	±	+	−
Spherical† refractive error	≥6	>−2‡	>−2‡	≤−2§	>−2‡
Axis of‖ cylinder	≥6	Horizontal	Horizontal	Vertical or oblique	Horizontal
Posterior subcapsular cataracts in both eyes	20-39	±	±	+	−
Bone spicule¶ pigmentation	6-19	−	±	+	+
History of parental consanguinity	≥6	−	+	−	±
Onset of night-blindness by history by age 20 yrs	—	+	−	+	−

*DOM indicates dominant; AR, autosomal recessive; XL, X-chromosome-linked; ISO, isolate. + indicates present; −, absent; ±, inconclusive.
†In the less myopic eye.
‡Includes hyperopic, plano, and myopic errors up to but not inclusive of −2.0 diopters.
§Includes all myopic errors of 2.0 diopters or greater.
‖Applies to those patients with cylindric refractive error ≥ 1.0 diopter in both eyes.
¶Bone spicule pigmentation present in all four quadrants in both eyes.

patients with X-chromosome-linked retinitis pigmentosa differed significantly from the prevalences in autosomal dominant, autosomal recessive, and isolate groups of patients, respectively. Although spherical refractive errors could be used to help separate different types of retinitis pigmentosa, it has yet to be established whether the magnitude of the spherical refractive error can be used to identify which relatives of affected patients are more likely to have retinitis pigmentosa.

Based on data from 35 families, the normal relatives in the autosomal dominant, autosomal recessive, X-chromosome-linked, and isolate groups, as a whole, differed significantly from their affected relatives with respect to best corrected visual acuity in the eye with better visual acuity and cylindrical refractive error in the eye with less astigmatism. Similar trends were observed within the four groups. Specifically, normal relatives characteristically had best corrected visual acuities of 6/7.5 (20/25) or better in the eye with better visual acuity and astigmatic errors, based on a cycloplegic refraction, of < 1.0 diopter in the less astigmatic eye. Therefore, relatives 6 years or older with corrected visual acuity of 6/9 (20/30) or

worse in the eye with better visual acuity or an astigmatic refractive error of ≥ 1.0 diopter in the less astigmatic eye are at greater risk for being affected than those relatives without these abnormalities. These findings provide some guidelines as to which relatives of affected patients, particularly between ages 6 and 19 years, should be screened for early retinitis pigmentosa with a careful ophthalmoscopic examination and ERG testing. Asymptomatic patients under age 20 years can have the early stages of retinitis pigmentosa, defined by the ERG, even though the ophthalmoscopic examination appears normal.[5,10,15-18]

These analyses are based on a population with retinitis pigmentosa who have had their diagnoses established on the basis of subnormal and delayed or nondetectable full-field ERGs.[10] Additionally, findings from routine ocular examinations that were risk factors in this study cannot be used alone to establish the genetic type of an affected patient or to determine that a relative is either normal or affected. However, the present study shows that certain findings in a routine ocular examination can be considered risk factors that have discriminating value both for genetic typing of affected patients and for identification of relatives at higher risk for having the early stages of retinitis pigmentosa. The weighting of these risk factors relative to each other and their independence from each other are currently being evaluated by statistical techniques including multiple discriminant analysis.

Summary

An outpatient population with retinitis pigmentosa was evaluated with respect to best corrected visual acuity, cycloplegic refractive error, appearance of the lenses, presence or absence of bone spicule pigmentation, age of onset of night blindness by history, and presence or absence of a history of parental consanguinity. The population included 489 affected patients subdivided into the four following groups: 69 (14.1%) dominant, 67 (13.7%) autosomal recessive, 34 (7.0%) X-chromosome-linked, and 319 (65.2%) isolate. Contingency table and life table analyses showed that significant differences existed for these criteria among the various groups. An analysis based on data from 35 families showed significant differences with respect to best corrected visual acuity and cylindrical refractive error when comparing affected patients with their age-matched normal relatives. These findings support the idea that observations in a routine ocular examination can aid in genetic classification of affected patients and in selection of relatives of affected patients who are at higher risk for having early stages of retinitis pigmentosa.

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REVERSIBLE NIGHT BLINDNESS ASSOCIATED WITH INTESTINAL BYPASS SURGERY

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Lipner[1] stated that the first successful massive intestinal resection was reported in 1881. More recently, small intestinal bypass procedures have assumed a role in the management of morbid obesity. Chronic diarrhea, liver failure, hypokalemia, hypocalcemia, and hypomagnesemia are well-recognized complications that may occur after intestinal bypass surgery.[1-4] Vitamin deficiencies, however, are thought to be uncommon after this type of operation,[3] and only recently iatrogenic night blindness associated with a decreased vitamin A level after intestinal bypass surgery has been recognized.[5] We describe the case of a 33-year-old man who developed severe night blindness secondary to vitamin A deficiency 3½ years after undergoing a jejunocecal bypass to reduce his obesity.

CASE REPORT

A 33-year-old man complained in May 1979 of great difficulty seeing at night for several days. Three and one half years previously he weighed 157.5 kg and at that time underwent jejunocecostomy to reduce his obesity. The jejunum was divided 30 inches distal to Treitz's ligament and anastomosed to the cecum in an end-to-side fashion. By the time the patient developed night blindness he weighed 67.5 kg. He was chronically distressed by mild to moderate diarrhea, and in March 1979 required hospitalization for correction of magnesium and zinc imbalances. There was no history of routine vitamin supplementation.

On initial ocular examination his visual acuity was 6/6 (20/20) in each eye. Slit-lamp examination of the right eye showed several small transparent vesicular inclusions, suggestive of a Bitot's spot, in the superficial conjunctiva and a small pannus of blood vessels growing up into the cornea from the inferior corneoscleral limbus. No xerosis of the cornea or the conjunctiva was evident. External examination of the left eye was normal. Ophthalmoscopic examination showed subtle pigmentary changes in the foveal area of each eye, probably compatible with a normal brunette fundus, and otherwise was unremarkable.

Intravenous fluorescein angiography was normal in both eyes. The initial threshold of his dark adaptation was increased (Fig. 1) and a biphasic component to the curve was absent, indicating that both cone and rod function was abnormal. Electroretinography (ERG) showed a mild reduction of a- and b-wave amplitudes in the light adapted state and a marked reduction of the same in the dark adapted state (Fig. 2). The visual field in each eye by Goldmann perimetry was constricted to a 10-degree central area with the IV_4e isopter using a white test object. The serum carotene level was 6 μg/dl (normal, 60-260 μg/dl).

The patient was believed to have night blindness because of vitamin A deficiency. Treatment was initiated with 25,000 I.U. of water-miscible vitamin A orally four times daily, 50 mg of magnesium oxide orally twice daily, and a nonzinc multivitamin (Theragran) daily.

He was next seen three days after initiation of therapy, at which time he reported a "sudden visual recovery." Visual acuity remianed 6/6 (20/20) in each eye and results of slit-lamp and ophthalmoscopic examinations were unchanged. Dark adaptation (Fig. 3) showed a normal biphasic curve, indicating a return of photoreceptor function. The ERG was normal in the light and dark adapted states (Fig. 4) and visual fields were full. The patient has not returned for re-examination.

DISCUSSION

Vitamin A deficiency may occur secondary to inadequate dietary intake,[6] but it has also been recognized in association with malabsorption states, such as those seen with celiac sprue and regional enteritis.[7] Recently, Partamian, Sidrys, and Tripathi[5] documented a case occurring secondary to jejunoileal bypass surgery. As vitamin A and its precursor, carotene,

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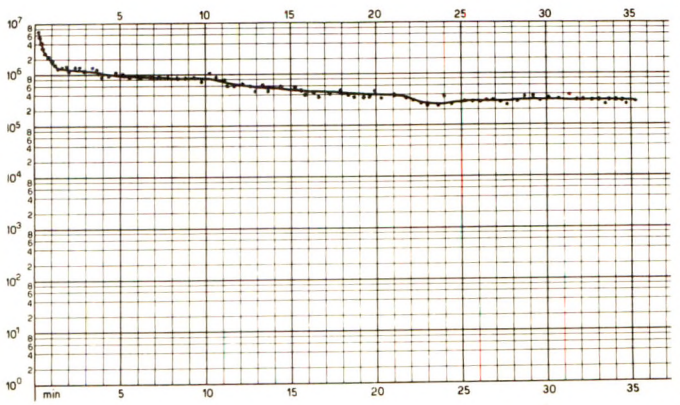

Fig. 1 (Brown, Felton, and Benson). Abnormal dark adaptation curve of the right eye, performed on the Goldmann/Weekers adaptometer, of patient with night blindness occurring 3½ years after intestinal bypass surgery. The y-axis represents the log luminance threshold for a fixed light stimulus to be seen and the x-axis depicts the time elapsed in the darkened state after a ten-minute period of light adaptation. An initial increased stimulus threshold of $10^{6.7}$ log units is present (normal, $10^{5.0}$ to $10^{6.4}$ log units). There is a rapid increase in sensitivity over the first two minutes, corresponding to cone adaptation, but no distinct evidence of increasing sensitivity of the rods. The final threshold was increased at $10^{5.3}$ log units (normal, $10^{1.2}$ to $10^{2.0}$ log units). A similar dark adaptation pattern was seen in the left eye.

are absorbed mainly in the small intestine,[8,9] a procedure such as intestinal bypass might be expected to decrease area for absorption and predispose the patient to the development of vitamin A deficiency.

Vitamin A is stored primarily in the liver and cirrhosis of this organ can also lead to the deficiency state.[10] Fatty degeneration of the liver[11] and cirrhosis[4] have been described after bypass surgery and may have a role in vitamin A deficiency. Retinol binding protein, a plasma vitamin A transport protein, is also decreased in patients with hepatic disease.[10]

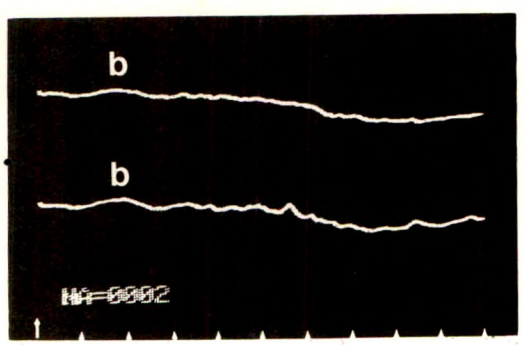

Fig. 2 (Brown, Felton, and Benson). Electroretinogram obtained after 15 minutes in the dark-adapted state at a low intensity stimulus before any therapy. The upper line represents the right eye, and the lower line represents the left eye. A minimal b-wave (b) is present in each eye and measures 13 μV in the right eye and 20 μV in the left eye. The arrow designates the flash stimulus and the distance between each small marker corresponds to a 20-msec period.

Abnormal dark adaptation is thought to be the first symptom of vitamin A deficiency.[6] Without vitamin A the visual pigments of rods and cones cannot be synthesized.[12] As was seen in our patient, however, rod function is much more severely affected, as evidenced by total loss of the second phase of the normally biphasic dark adaptation curve. Cone function is diminished, but early impairment appears to be insufficient to cause a decrease in visual acuity. Zinc deficiency, in the presence of normal vitamin A levels, has also been identified as a cause of abnormal dark adaptation,[13] but the absence of zinc in the therapeutic regimen of our patient precludes this as a prominent causal factor.

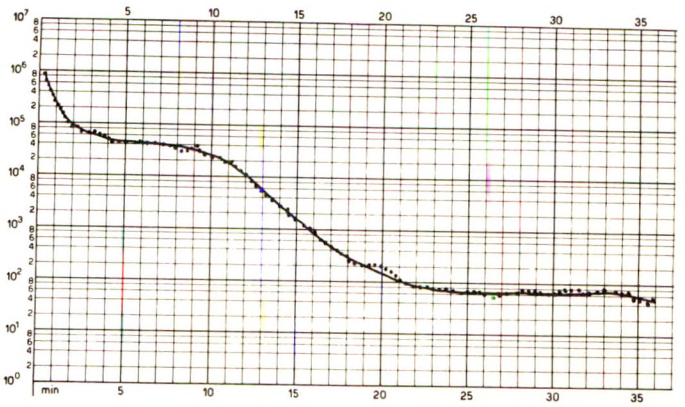

Fig. 3 (Brown, Felton, and Benson). Normal biphasic dark adaptation curve of the right eye of our patient after three days of oral vitamin A therapy. The initial threshold stimulus for cones has decreased (see Fig. 1) and from ten to 20 minutes there is a marked increase in sensitivity, corresponding to functioning rods.

The rapid reversal of the dark adaptation curve to normal in our patient is not surprising, as impaired dark adaptation has been reported to return to normal in a patient with celiac disease within six hours after orally administered vitamin A and one hour after intramuscular injection.[14]

Ocular findings described with vitamin A deficiency include conjunctival and corneal xerosis, foamy conjunctival lesions (Bitot's spots), corneal vascularization, keratomalacia in severe cases,[6] and discrete yellow dots in the midperiphery of the fundus.[15,16] These findings may or may not be present, depending upon the severity of the deficiency, and probably develop after abnormal dark adaptation. A Bitot's spot, as noted in our patient, may be related to generalized malnutrition, rather than specifically to vitamin A deficiency.[17]

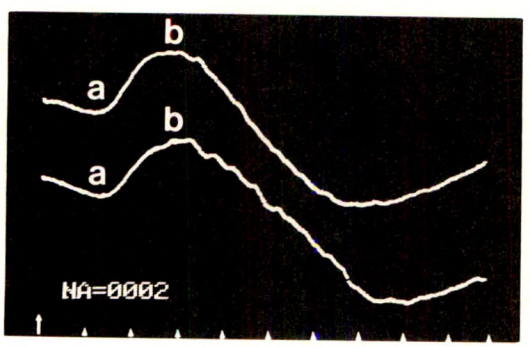

Fig. 4 (Brown, Felton, and Benson). Normal ERG after 15 minutes in the dark-adapted state at low intensity stimulus after three days of oral vitamin A therapy. An a-wave (a) is now present in each eye, as well as a prominent b-wave (b), indicating a return of photoreceptor function. The amplitude of the b-waves has increased substantially to 184.0 μV in each eye (see Fig. 2). As in Figure 2, the arrow designates the flash stimulus and the time elapsed between the markers is 20 msec.

Electroretinography in vitamin A deficiency shows first a disappearance of the a-wave, followed by the b-wave, as the depletion state becomes more severe.[18] In our case the scotopic ERG was affected to a greater extent than the photopic ERG, again indicating more marked involvement of rods over cones in this entity.

Histopathologic examination of animal eyes with vitamin A deficiency initially shows disorganization of rod outer segments.[18] As the disease progresses, the outer segments and eventually whole visual cells disappear. Although outer segments may regenerate after vitamin A supplementation, at some point the cells are irreparably damaged, indicating that this is a potentially visually irreversible condition. Therefore, the entity of night blindness secondary to vitamin A deficiency after intestinal bypass surgery should be recognized by the clinician as early as possible.

Summary

A 33-year-old man had a sudden onset of night blindness 3½ years after intestinal bypass surgery for morbid obesity. Ocular examination disclosed a probable Bitot's spot and electrophysiologic testing showed markedly impaired dark adaptation and subnormal electroretinography. After therapy with orally administered vitamin A, the night blindness disappeared and the dark adaptation curve and electroretinogram returned to normal.

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HISTOPATHOLOGY IN THE IRIS-NEVUS (COGAN-REESE) SYNDROME

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Cogan and Reese[1] and others[2,3] have described patients with a syndrome characterized by unilateral glaucoma in eyes with peripheral anterior synechiae, multiple iris nodules, and ectopic Descemet's membrane. Scheie and Yanoff[4] described 14 patients with this iris-nevus syndrome. These authors, however, stressed a more diverse clinical appearance in which glaucomatous eyes had a spectrum of clinical findings. In addition to the triad of anterior synechiae, iris nodules, and ectopic glass-like membrane, abnormalities included corneal edema, stromal iris atrophy, iris pigment epithelial atrophy, ectropian uveae, and ectopic pupil.

We describe another patient with unilateral glaucoma and clinical findings identical to those originally described by Cogan and Reese.[1]

CASE REPORT

A 23-year-old woman underwent bilateral cataract surgery at the age of 5 years. Records from this period were unavailable; however, the patient recalled complications involving some "herniations" in the left eye after surgery. She had frequent episodes of pain and redness that subsided spontaneously.

The patient was seen in consultation at the Bascom Palmer Eye Institute on April 24, 1978. Visual acuity was R.E.: 6/7.5 (20/25) and L.E.: 6/60 (20/200). Both pupils were somewhat eccentric and distorted superiorly. There was an afferent pupillary defect involving the left eye.

The right eye was surgically aphakic with a clear cornea, normal iris, and intraocular pressure of 15 mm Hg. In the left eye, there were areas of subconjunctival uveal incarceration with mild staphyloma formation seen at the superior corneoscleral limbus. Results of the examination of the cornea, including specular biomicroscopy of the corneal endothelium, were normal. In the midportion of the iris, elevated pigmented nodules were present in the geographic areas of depigmented iris (Fig. 1). Glistening highlights reflected from a glass-like membrane covering the iris surface. At the pupillary margin, the iris was adherent to the posterior capsule and cortical lens remnants. No iris defects were noted. Applanation pressure was 28 mm Hg.

The visual field (Goldmann perimeter) in the right

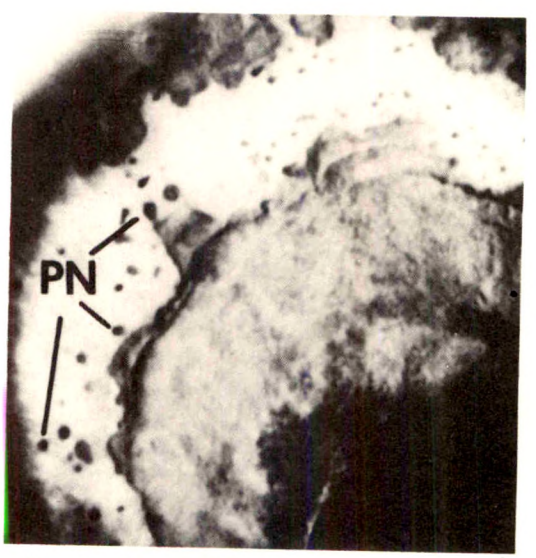

Fig. 1 (Radius and Herschler). Preoperative photograph of the involved eye. Extensive geographic areas of depigmented iris stroma are evident in the midperipheral iris. Numerous pigmented nodules (PN) are present in this region. A refractile cellophane-like membrane could be seen clinically to cover the iris surface in this area.

From the Eye Institute, Medical College of Wisconsin, Milwaukee, Wisconsin (Dr. Radius); and the Bascom Palmer Eye Institute, University of Miami, Miami, Florida (Dr. Herschler). This study was supported in part by funds from Ophthalmic Research Center Grant EY-01931 and Research Grant EY-20436, National Eye Institute, Bethesda, Maryland, and Research to Prevent Blindness, Inc.

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eye was full. In the left eye there was marked nasal constriction to within 5 degrees of fixation as well as superior arcuate loss of visual function. Gonioscopic examination of the right eye showed anterior synechiae of the iris superiorly at the cataract incision. The angle was completely closed in the left eye by iridocorneal adhesions. The optic nerve head in the right eye appeared healthy with a round cup (cup to disk ratio of 0.4). The optic nerve head in the left eye was almost totally cupped.

The patient underwent trabeculectomy, sector iridectomy, and anterior vitrectomy in the left eye on June 6, 1978. The surgical specimen included an internal lamellar block resection of cornea, corneoscleral meshwork, iris root, and anterior ciliary body. Continuity between this tissue block and the iris specimen from the sector iridectomy was maintained. The surgical specimen was flattened on a dry filter paper and immersed in buffered (pH 7.4) 4% gluteraldehyde. Twenty-four hours later, the specimen was postfixed in osmium tetroxide and embedded in epoxy resin (Epon) for sectioning. Specimens 2 μ in thickness were cut such that the plane of section was perpendicular to the iris surface and parallel to the long axis of the tissue block. Step sections were taken at each 50 μ, air dried, and then stained with paraphenylene diamine. Slides were examined by phase contrast microscopy.

Thin sections were selected from a region of the original specimen to include both anterior and posterior iris surfaces. These sections were counterstained with uranyl acetate and lead nitrate, and examined by transmission electron microscopy.

RESULTS

The surgical specimen consisted of a strip of iris measuring 1 × 2 × 4 mm that was attached to a block of internal lamellar cornea, corneosclera, and anterior ciliary body that measured 1 × 2 × 3 mm. The lamellar resection of the inner eye wall was hinged at the iris root with the endothelial corneal surface opposed to the anterior iris plane.

At one end of the specimen, peripheral cornea and the termination of Descemet's membrane was identified. The anterior chamber angle was obliterated and normal trabecular structures could not be identified. The corneoscleral tissue and Descemet's membrane were in direct contact with the iris stroma, which was consistent with synechial closure of the angle noted clinically. No corneal endothelium could be identified in this region.

In the midportion of the iris specimen, a cuticular membrane was identified closely opposed to the normal iris stroma (Fig. 2). Only scattered cell fragments containing pigment granules could be identified on the anterior surface (anterior chamber) of this membrane. The membrane extended from a point at the border between the outer and middle third of the iris surface to within 1 mm of the pupillary margin. No continuity between this structure and Descemet's membrane was shown in these sections.

This area of the specimen corresponded to the smooth, hypopigmented region of the iris noted clinically (Fig. 1). Iris nodules, seen preoperatively in this same region could be identified in several of the step sections examined (Fig. 2). Although there was an increase in pigmentation, these nodules consisted of apparently normal iris stroma. In most instances, nodules pierced the cuticular membrane, which surrounded the neck of the peduncle. In some instances the membrane appeared to cover most of the iris nodule. In isolated specimens the membrane covered the iris peduncles completely. Near the pupillary margin the membrane ended abruptly in a region of pigmented, clumped iris stroma.

On the posterior iris surface, a third cuticular membrane was identified (Fig. 3). In some areas this membrane was closely adherent to iris pigment epithelium. More distant from the pupillary margin the structure was free floating and terminated in a collection of amorphous material. A monolayer of cuboidal cells was on the posterior surface (posterior chamber) of this membrane (Fig. 3). These cuboidal cells were pale staining and vacuolated with apically located nuclei. No continuity between this posterior membrane and that seen on the anterior iris surface or Descemet's membrane could be shown in any of these sections.

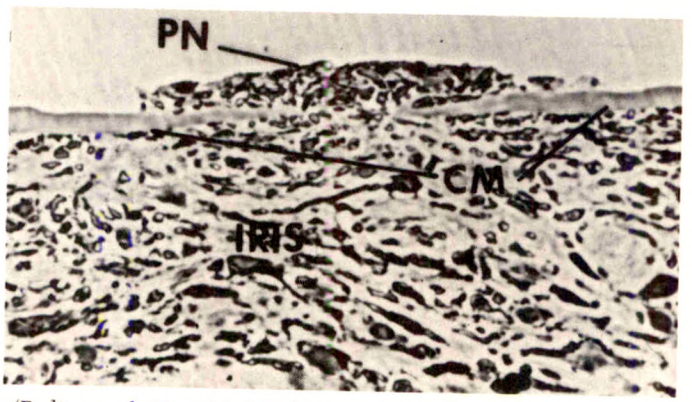

Fig. 2 (Radius and Herschler). Phase-contrast photomicrograph of the surgical specimen. A cuticular membrane (CM) can be seen closely opposed to the iris surface. This membrane extended from the border between the lateral and middle thirds of the iris to within approximately 1 mm of the pupillary margin. At several points along the anterior surface of the iris, collections of pigmented iris stromal cells can be seen anterior to the cuticular membrane. These correspond to the iris nodules (PN) noted clinically (paraphenylene diamine, ×300).

Specimens examined by transmission electron microscopy were selected from a region that allowed examination of both the anterior and posterior iris membranes (Fig. 3). Beneath the anterior membrane, normal iris stroma cells containing pigment granules could be identified. The membrane was amorphous and tightly opposed to the iris stroma (Fig. 4). The anterior surface of the membrane had many villous projections. Scattered cell fragments, some contain-

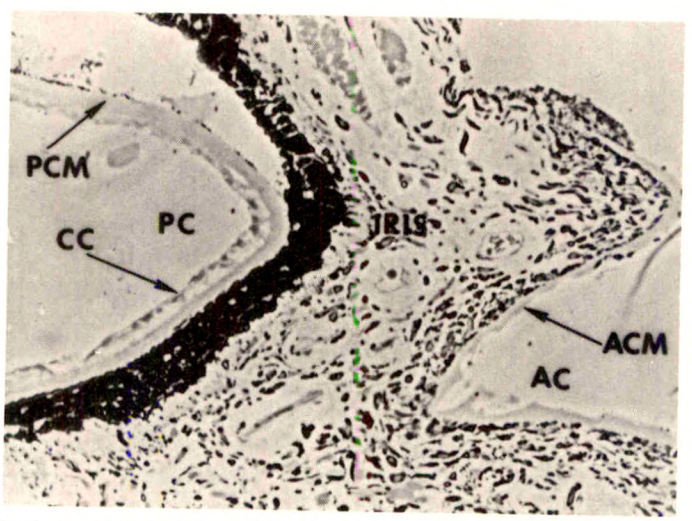

Fig. 3 (Radius and Herschler). Phase-contrast photomicrograph of surgical specimen. On the posterior surface (PC, posterior chamber) of the iris, another cuticular membrane (PCM, posterior cuticular membrane) can be identified closely adherent to the iris pigment epithelium at least in some regions of the specimen. A single layer of cuboidal cells (CC) is adherent to the posterior surface of this membrane. No continuity between this membrane and that on the anterior surface of the iris (ACM, anterior cuticular membrane; AC, anterior chamber) or Descemet's membrane could be established (paraphenylene diamine, ×200).

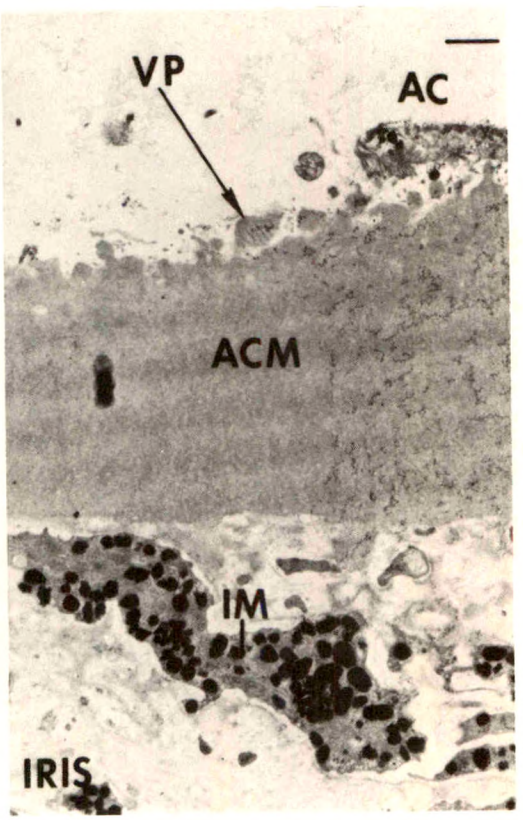

Fig. 4 (Radius and Herschler). Electron photomicrograph of the anterior surface of the iris of the surgical specimen. A cuticular membrane (ACM, anterior cuticular membrane) can be identified closely opposed to the iris surface. This membrane is amorphous in appearance. Villous projections (VP) are present along the exposed surface (AC, anterior chamber). No cellular layer is associated with this anterior membrane; iris melanocyte (IM) (×6,500) (bar gauge = 1 μ).

ing pigment granules, were seen at several points along the surface of this membrane but no continuous cell layer was associated with the structure.

In some areas, the posterior membrane was in contact with normal iris pigment epithelium. By electron microscopy, this membrane also appeared amorphous except for a lamellar splitting near to the iris surface (Fig. 5). In this region a fibrillar (10 nm) structure to the membrane was identified. The membrane interdigitated with villous processes of the iris pigment epithelium. No basement membrane material was identified.

The opposite surface of this glass-like structure was in contact with the monolayer of cuboidal cells noted by light microscopy. No basement membrane material was noted; however, there was extensive interdigitation of terminal cell processes at the interface between monolayer and cuticular layer (Fig. 6). The cytoplasm of the cell layer showed hydropic changes. Moderately dense staining nuclei, mitochondria, and cytoplasmic filaments were noted. No desmosomal structures were identified.

Discussion

Typical of the cases originally described by Cogan and Reese,[1] our patient had unilateral glaucoma with extensive peripheral anterior synechiae and multiple iris nodules. A glass-like membrane covering the anterior iris surface was noted both clinically as well as histologically. It has been suggested that this cuticular membrane is significant with respect to the cause of this syndrome.[1,4,5]

Other clinical entities characterized by iris changes and glaucoma have been described. For example, essential progressive atrophy of the iris is characterized by a unilateral often intractable glaucoma associated with progressive iris atrophy leading to pseudopolycoria, ectopic pupil, and extensive peripheral anterior synechiae.[6-8] In contrast, eyes with Chandler's syndrome have mild iris atrophy but no pseudopolycoria, scattered peripheral anterior synechiae, and unilateral glaucoma.[9] Corneal decompensation, presumably secondary to an associated endothelial dystrophy, often occurs at relatively mild pressure increases and dominates the clinical symptomatology.

Recently, similarities rather than dif-

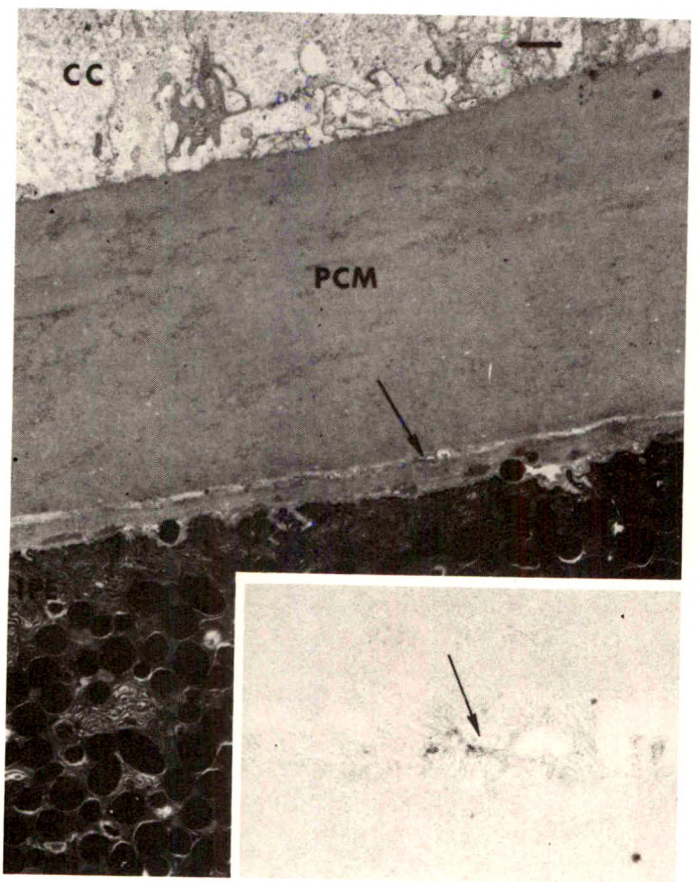

Fig. 5 (Radius and Herschler). Electron photomicrograph taken of the surgical specimen. The posterior cuticular membrane (PCM) is seen to be closely adherent to the iris pigment epithelium (IPE). The opposite surface of this membrane is lined by a monolayer of cuboidal cells (CC) (×5,000). The membrane is uniform in density except in one area of lamellar splitting near the iris pigmented epithelium. In this region, a fibrillar nature (10 nm) of this membrane is evident (arrow) (×30,000) (bar gauge = 1 μ).

ferences between these three syndromes have been stressed.[5,10] Iris nodules have been noted in eyes with essential iris atrophy,[11] and iris atrophy has been described in eyes with the iris-nevus syndrome.[4] All three clinical entities have ectopic Descemet's membrane covering parts of the iris surface and anterior chamber angle as part of the disease process.[1-5,10-14]

It is unclear whether this overlap in symptomatology and histopathology reflects individual variation in a single disease process or the limited ability of certain ocular tissues, such as the iris and cornea, to respond to a similar yet distinct tissue insult. However, it has been suggested that all three of these clinical entities—Chandler's syndrome, essential iris atrophy, and iris-nevus syndrome—have a single underlying cause.[5,14] It has been hypothesized that corneal endothelial degeneration and accompanying ectopic endothelial membranes are responsible for occlusion of the filtration meshwork and subsequent pressure increase. Iris nodules, described in both the iris-nevus[1-3] syndrome and essential iris atrophy[11] are suggested to have been caused by the spread of this membrane across the iris surface.[2,5] In support of this supposition, iris nodules have been limited to the region of iris involved by the ectopic membrane, except in one instance.[1,4,5,11]

Our case, in part, supports this hy-

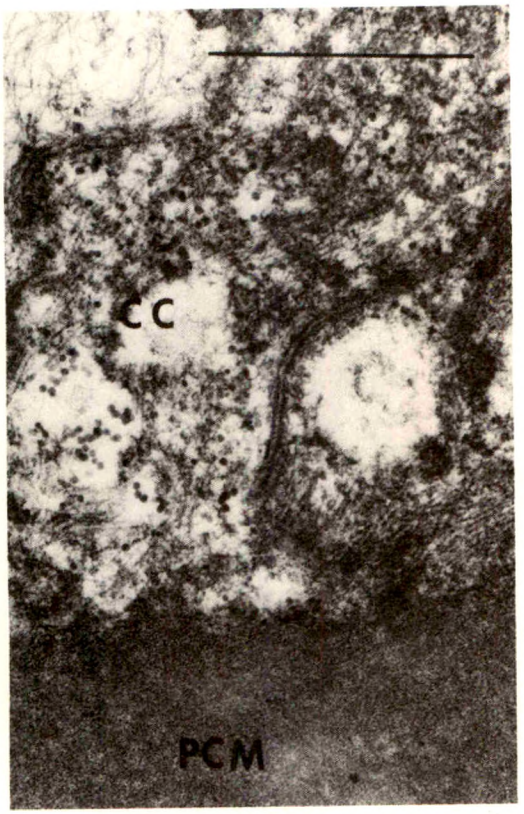

Fig. 6 (Radius and Herschler). Electron photomicrograph taken of the surgical specimen in the region of the posterior cuticular membrane. The monolayer of cuboidal cells (CC) is closely adherent to the posterior cuticular membrane (PCM) lying along the iris surface. There is no banding pattern or subepithelial stromal tissue associated with this membrane. The cuboidal cells (CC) contain hydropic cytoplasm with interdigitating cell processes at the surface of the membrane. No true desmosomal structures were identified (×30,000) (bar gauge = 1 μ).

pothesis. Iris nodules in this patient's eye consisted of aggregates of iris stroma cells surrounded by ectopic cuticular membrane as described in previous reports. However, no communication between this ectopic membrane and Descemet's membrane could be established in this specimen. Electron microscopy showed that this membrane lacked the characteristic banding as well as the subcellular tissue changes, which, in a previous specimen, suggested metaplasia of corneal endothelium as the most likely source of such structures.[12] Additionally, in the present case, no endothelial dystrophy was noted even by specular microscopic examination of the cornea. Although eyes with the iris-nevus syndrome can occasionally have corneal decompensation, even at only moderate pressure increase, clinical evidence of endothelial disease has not been characteristic of this entity.[1-4,9,15,16]

The origin of the ectopic membrane in the present case is perhaps critical to understanding the pathogenesis of this disease process. Possibly the membrane is contiguous with part of the corneal endothelium and Descemet's membrane in some part of the eye unavailable for histologic examination in this surgical specimen. Perhaps an associated endothelial layer may have been lost during fixation or surgical manipulation. The corrugated surface of the structure suggests that some cellular layer had been in contact with the membrane previously. The nature of these surface changes is similar, however, to that seen at the interface between the membrane and monolayer of cells lining the posterior iris surface. However, the origin of this posterior membrane is not certain. It is unusual for ectopic endothelial membranes to involve the posterior aspect of the iris, but this possibility cannot be eliminated. Alternatively, both anterior and posterior cuticular membranes may have originated from retained lens material. A third possibility is that one or both ectopic membranes could have originated from metaplastic changes in the iris stroma itself. Previous surgical trauma could have triggered iris metaplasia that produced the clinical appearance described in the present case.

If the cuticular changes in this patient had originated from metaplastic endothelium and an associated subclinical endothelial dystrophy, then the present

case would support the hypothesis that similarities in these various clinical entities reflect a common cause. The spectrum of disease might depend upon whether the cornea (Chandler's syndrome) or the iris abnormality (essential iris atrophy or iris-nevus syndrome) predominate. However, because the corneal endothelium appears normal in the present case, the membrane, iris nodules, and unilateral glaucoma in this eye morelikely originated from metaplastic changes in iris or lens tissue. The clinical appearance common to all three diseases may reflect limited ability of certain ocular tissues to respond to diverse insults as well as the inability to distinguish between various causes when examination is performed at a late stage in the disease process.

Until the question of origin has been clarified, it seems reasonable to maintain semantic distinctions between these various clinical syndromes both because of differences in prognosis and management, and because of the need to correlate future clinical and histologic data in an effort to define what pathogenic differences in these entities do exist.

Summary

A 23-year-old-woman had iris-nevus (Cogan-Reese) syndrome characterized by unilateral glaucoma with peripheral anterior synechiae, multiple iris nodules, and ectopic Descemet's membrane. A surgical specimen excised from the involved eye was examined by light and electron microscopy. A cuticular membrane covered both the anterior and posterior surfaces of the iris in this specimen. On the anterior surface of the iris, many projections of apparently normal iris stroma pierced or were surrounded by this membrane. On the posterior surface of the iris, this membrane was associated with a monolayer of cuboidal cells.

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REDUCTION OF ENDOTHELIAL CELL LOSS DURING PHAKIC PENETRATING KERATOPLASTY

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In a previous study of endothelial cell loss during penetrating keratoplasty, three times more cell loss was noted in phakic transplants than in aphakic grafts.[1] This loss was attributed to rubbing by the recipient iris and lens during the initial graft placement and to the anterior chamber being more shallow (or absent) in phakic transplants as compared with that in aphakic transplants. After the increased endothelial cell loss in phakic grafts was discovered, more attention was paid to forward pressure on the recipient iris and lens during the procedures and to the softness of the eye before operation. I report my experience with endothelial cell loss in 30 subsequent corneal transplants.

SUBJECTS AND METHODS

In 32 consecutive penetrating keratoplasties, 30 had endothelial photographs taken before and within seven days after transplantation. Of the two additional transplants performed during the same period, one had the postoperative photographs taken three months after the operation and the other transplant was replaced on the second postoperative day with an anterior vitrectomy because of aphakic pupillary block. Before keratoplasty all donor corneas were put into a special corneal storage container[2] in which the cornea was kept at 4°C in McCarey-Kaufman medium[3] containing 100 units/ml of penicillin-streptomycin solution. The donor endothelium was observed and photographed through the closed storage container with a modified specular microscope.[2] All donor eyes were removed within five hours of the death of the donor, and all donor corneas were placed in the storage containers within seven hours after enucleation and stored for periods ranging from three to 124 hours (mean, 47 hours) before transplantation. Donor ages ranged from 10 to 72 years (mean, 41.5 years).

Various combinations involving preoperative digital ocular massage, intravenously administered mannitol, and scleral rings were used with the phakic transplants in an attempt to decrease the forward pressure on the lens and iris. When used, the ocular massage was performed for ten minutes, 1 to 2 g/kg of body weight of mannitol was administered intravenously during a 15- to 30-minute period preceding the operation, and a double Flieringa-LeGrand scleral ring was used. Of the 15 phakic grafts, a scleral ring was used in ten, mannitol in four, and massage in seven. A scleral ring and massage were used also in all combined cataract extraction and keratoplasty procedures, as was done in the first study.[1]

Anterior vitrectomies were performed with the Kaufman Vitrector II in nine cases. The recipient trephine incisions in the 15 phakic transplants ranged from 7.0 to 8.5 mm. In six of the phakic grafts, a donor incision 0.25 or 0.5 mm larger than the recipient incision was used. In all 15 aphakic transplants (that includes combined keratoplasty and cataract extraction), an 8.0-mm donor button was placed in a 7.5-mm recipient opening.

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The donor endothelium was examined and photographed again with a clinical specular microscope[4] within one week after transplantation, and the central graft thickness was measured with the same instrument.[1,5] At least three endothelial photographs from each examination were then projected onto transparent Mylar sheets, and tracings by hand were made with black ink. Only clearly visible cell margins were traced. The individual cell areas and cells per square millimeter were determined with a computer image-processing system developed here.[6] An average of 173 cells per cornea was measured for each examination. The central endothelial cell loss, given as a percentage of the preoperative cell count, was calculated by comparing the preoperative and postoperative densities of the central endothelial cells (cells/mm^2) for each cornea. Different variables were compared by use of either the rank-sum test or Spearman's rank correlation (ρ) corrected for ties; $P<.05$ was considered to be statistically significant.

Results

The mean endothelial cell loss for all 30 transplants was 15.6%, and there was no significant difference between the 15 phakic (mean loss, 14.9%) and the 15 aphakic (mean loss 16.3%) grafts. The phakic and aphakic (that includes combined cataract extraction and keratoplasty) transplants did differ significantly in two respects: (1) recipient age (mean phakic age, 44 years; mean aphakic age, 74 years; $P < .01$) and (2) corneal thickness (mean phakic, 0.63 mm; mean aphakic, 0.69 mm; $P < .05$). The phakic and aphakic grafts did not differ significantly with respect to preoperative and postoperative cell count, cell loss, number of days postoperative, donor age, storage times, or graft size. In all 30 patients, the cell loss was directly correlated with the postoperative corneal thickness ($\rho = 0.62$, $P < .001$), but was not correlated with the preoperative cell count, donor age, storage time, or graft size. An anterior vitrectomy did not significantly affect the cell loss or postoperative corneal thickness, whether the nine combined procedures or all 15 aphakic grafts were considered. The preoperative endothelial cell density (range, 1,848 to 3,595 cells/mm^2; mean, 2,769 cells/mm^2) was significantly associated with donor age ($\rho = -0.55$, $P = .001$).

The 15 phakic transplants in this study were too few to analyze statistically with regard to operative techniques to decrease forward pressure on the recipient iris and lens. However, when the results were combined with those from the 11 patients in the previous study[1] who had endothelial photographs taken during the first postoperative week (Table), certain comparisons became meaningful. Although the use of a double scleral ring or intravenously administered mannitol did not significantly affect mean endothelial cell loss, the eight patients who had preoperative digital ocular massage had significantly less cell loss ($P < .03$) than did the 18 who did not. Among the 18 patients who did not have massage, however, the cell loss was significantly increased only in the ten in whom a double scleral ring was also used ($P < .001$). There was no significant difference in mean cell loss between the eight patients who had neither scleral ring nor massage and the eight patients who had both.

Discussion

The most important finding in this study was the elimination of increased endothelial cell loss in phakic transplants. Oversized donor tissue and preoperative massage were the only substantial variations in surgical technique between this study and an earlier study.[1] Oversized donor grafts were not used in the former study,[1] but were used in

TABLE

MEAN ENDOTHELIAL CELL LOSS ACCORDING TO TECHNIQUE USED IN 26 PHAKIC CORNEAL TRANSPLANTS

Technique Used				
Scleral Ring	Intravenous Mannitol	Digital Massage	No. of Transplants	Cell Loss (%)
No	No	No	6	17
No	Yes	No	2	15
Yes	No	No	2	32
Yes	Yes	No	8	36
Yes	No	Yes	7	13
Yes	Yes	Yes	1	6

all of the aphakic and nearly one half of the phakic grafts in the present study. Placing a donor button that is 0.25 or 0.50 mm larger than the recipient incision may give more clearance between the graft endothelium and the recipient iris and lens, thus producing less endothelial cell loss. However, the six phakic grafts with oversized donors had cell loss more than twice that of the nine phakic grafts with donors of equal recipient size, although this difference was not statistically significant.

Thus, preoperative digital ocular massage probably accounted for the observed elimination of increased endothelial cell loss in phakic transplants, because massage softens the globe[7] and could be expected to decrease the forward pressure on the iris and lens in a subsequently opened eye. Intravenously administered mannitol also can soften the globe,[8] although it did not decrease cell loss in phakic grafts in this study. The simple preoperative technique of digital ocular massage may be used also in conjunction with other more complex keratoplasty techniques designed to avoid endothelial damage,[9-11] if the surgeon desires. This study confirms the results of Abbott and Forster,[12] who used massage in all patients and also found no difference in cell loss between phakic and aphakic grafts.

The use of a double scleral ring increased the mean endothelial cell loss in phakic transplants, unless preoperative digital ocular massage was also used. Only three of the ten phakic patients having a scleral ring without massage were in the present study, which may account for some of the decreased cell loss in the phakic grafts. This finding was consistent with the appearance of the commercially available Flieringa-LeGrand ring on the eye. The posterior ring is too small for most eyes, so that, if the anterior ring is sutured to the sclera, the posterior ring exerts inward pressure on the globe. This problem has subsequently been avoided by using a single Flieringa ring. Thus, part of the beneficial effect of digital ocular massage was to counteract the increased intraocular pressure caused by the double scleral ring. However, massage alone may also be useful in reducing endothelial cell loss in phakic transplants.

The increased corneal thickness in transplants that sustain more endothelial cell loss is possible because a more damaged endothelium would take longer to regain normal function. Increased corneal thickness in aphakic grafts was found also in the previous study, and it was suggested then that this effect was caused by more direct access to vitreous humor.

The present study showed no statistically significant difference in cell loss or

corneal thickness between the aphakic grafts with and without anterior vitrectomy. This confirms the results in the previous study[1] and one by Abbott and Forster,[12] who also found no significant change in cell loss with anterior vitrectomy. A vitrectomy instrument was used for both studies, although the photographs were taken at a later postoperative interval (12 weeks) in Abbott and Forster's study.

Endothelial cell loss was not correlated with graft size or with death to enucleation time, as it had been in the previous report.[1] Neither variable had a range of values in this study that was large enough to adequately test for an effect from these factors. The preoperative endothelial cell density was significantly correlated with donor age, as it was in the previous study and as it has been in previous reports of normal subjects.[1,4,13-20]

Summary

I studied the central donor endothelium of 30 clear, penetrating corneal transplants with a specular microscope before and within one week after keratoplasty. The mean endothelial cell loss was 15.6%, and there was no significant difference between the cell loss in phakic and aphakic transplants, as there had been in a previous study. Probably the decrease in endothelial cell loss in the phakic transplants was the result of the use of preoperative digital ocular massage, which softens the eye and decreases endothelial contact by recipient iris and lens during initial graft placement. The decreased use of a double scleral ring without preoperative massage also helped lower the cell loss. The postoperative corneal thickness, which was greater in aphakic transplants, also was significantly correlated with endothelial cell loss.

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NUMMULAR KERATITIS ASSOCIATED WITH INFECTIOUS MONONUCLEOSIS

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Infectious mononucleosis is a common disease with protean manifestations ranging from a subclinical infection to a severe disease that may affect many different organ systems, including the eye. The cause is the Epstein-Barr virus, which is a DNA, herpes type virus. Laboratory confirmation of the diagnosis is based on the two following serologic tests: (1) the heterophil antibody test, and (2) the indirect fluorescent antibody titer that detects the cell or viral antigens of the Epstein-Barr virus.

Tanner[1] divided the ocular manifestations of infectious mononucleosis into two groups: (1) those caused by direct involvement of the eye and its adnexae, and (2) those affecting vision and the neuro-ophthalmologic apparatus caused by a more remote lesion in the central nervous sytem. With respect to the direct involvement of the eye, infectious mononucleosis has been found to affect the eyelids, periorbital tissues, conjunctiva, episclera, cornea, uveal tract, retina, and optic nerve. There may be a mild or marked edema of the eyelids and periorbital areas.[2] Conjunctivitis is common and may occur early in the disease and be either of a follicular or membranous nature.[2,3] Subconjunctival hemorrhages may also be seen.[3] Nodular episcleritis[4] and uveitis[3] have been described. One patient had retinal hemorrhages, papillitis, and retinal edema.[5]

To the best of our knowledge, only one case of corneal involvement in infectious mononucleosis has been described. Payrau and Hoël[6] described a patient who developed both an epithelial and interstitial keratitis during an episode of suspected mononucleosis; however, the relationship between the two was not established and is uncertain. We describe a patient who had bilateral interstitial nummular keratitis associated with a severe case of infectious mononucleosis.

CASE REPORT

A 16-year-old boy developed a diffuse, intense, pruritic, erythematous macular rash involving his entire body. Two to three days later he saw his internist with complaints of anorexia, fatigue, fever, severe sore throat, swelling of his hands and eyelids, and photophobia. He had taken no medication before the onset of his illness. On physical examination, the patient's temperature was 38.6°C. There was marked injection of his conjunctivae in both eyes, as well as a fiery red inflammation of the oral mucosa and enlarged, inflamed tonsils without exudate. There were no enlarged lymph nodes or hepatosplenomegaly. The skin rash was present, but less intense than it had been earlier. Initial laboratory studies showed a white blood cell count of 17,700/mm^3 (73 neutrophils, 20 bands, 4 lymphocytes, 2 eosinophils, 1 monocyte, no atypical lymphocytes); serum glutamic oxaloacetic transaminase, 209 IU/L (normal, 10 to 40 IU/L); serum glutamic pyruvic transaminase, 103 IU/L (normal, 3 to 36 IU/L); alkaline phosphatase, 420 units/100 ml (normal, 30 to 100 units/100 ml); and

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normal lactate dehydrogenase and bilirubin. Throat cultures were negative. The heterophil antibody test (Monospot test) was positive. Antibody titers measured by complement fixation tests for herpes simplex, adenovirus, mumps, cytomegalovirus, influenza virus, and respiratory syncytial virus were all less than 1:8. Epstein-Barr virus titer (measured by indirect fluorescent antibody technique) was 1:256. An initial diagnosis of infectious mononucleosis was made, and the patient was admitted to the hospital. He was taking 60 mg of prednisone orally daily, which was tapered over a seven-day period, and then discontinued. The patient was discharged from the hospital after ten days, with relief of all symptoms except for the conjunctival injection and photophobia. No ophthalmic examination was done. At this time, the serum glutamic oxaloacetic transaminase was 90 IU/L and the alkaline phosphatase was 200 units/100 ml.

One week after his discharge, the patient reentered the hospital because of anorexia, fatigue, photophobia, and polyarthritis involving the elbows, wrists, and knees. His temperature was 40°C. On examination, he had hepatosplenomegaly and enlarged lymph nodes. An ophthalmic examination was performed. The patient had mild bulbar and tarsal conjunctival injection. The corneas were clear, there was no anterior chamber inflammation in either eye, and the retinas were normal on indirect ophthalmoscopic examination. Laboratory results showed white blood cell count of 14,200/mm^3 (92 neutrophils, 1 band, 7 lymphocytes, no atypical lymphocytes); serum glutamic oxaloacetic transaminase, 90 IU/L; serum glutamic pyruvic transaminase, 241 IU/L; alkaline phosphatase, 85,units/100 ml; and bilirubin, 0.4 mg/dl. Urinalysis, fluorescent antinuclear antibody, rheumatoid factor, latex agglutination test, and C-3 complement were normal. Antibody titers for herpes simplex virus, adenovirus, mumps, cytomegalovirus, influenza, and respiratory syncytial virus were again less than 1:8. The Epstein-Barr virus titer rose to 1:2048.

Sixty milligrams of prednisone orally daily was again prescribed, which was then tapered over a two-month period. All symptoms resolved, including the conjunctival injection and photophobia. The laboratory results also returned to normal and included the following: serum glutamic oxaloacetic transaminase, 15 IU/L; serum glutamic pyruvic transaminase, 107 IU/L; alkaline phosphatase, 88 units/100 ml; and bilirubin, 0.4 mg/dl. However, approximately one week before his last dose of corticosteroids, the patient had a recurrence of the conjunctival injection and photophobia without recurrence of other signs or symptoms. He came to our clinic three weeks after the recurrence of these symptoms, at which time he had not been taking corticosteroids for two weeks. His initial visual acuity was R.E.: 6/18 (20/60) and L.E.: 6/15 (20/50), correctable to 6/6 (20/20) in both eyes. The eyelids were normal. There were no palpable preauricular nodes. Tarsal and bulbar conjunctivae were normal in both eyes. Corneal examination showed a bilateral nummular interstitial keratitis without epithelial abnormality. The lesions were located around the entire 360 degrees of the peripheral cornea with sparing of the 0.5 mm between the lesions and the corneoscleral limbus, and the central 4 mm of the cornea. The lesions were gray-white, translucent, discrete, and coin shaped, varying in size from 0.3 to 0.5 mm and located at all levels of the stroma (Figure). Corneal sensation was normal in both eyes, as measured with an aesthesiometer. On slit-lamp examination, the anterior chamber showed no inflammation in either eye. Goldmann applanation tonometry was 14 mm Hg bilaterally. Results of dilated indirect ophthalmoscopic examination were normal in both eyes.

The patient was applying prednisolone 1%, one drop every two hours, and bacitracin-polymyxin ointment in each eye at bedtime. One week after this treatment was begun, the conjunctivae were clear bilaterally, and the corneal lesions had almost completely resolved. The prednisolone 1% was decreased to every three hours. On the next visit, two weeks after beginning treatment, the conjunctivae were clear, and the corneal lesions had completely disappeared. The corticosteroids were tapered during the next four weeks. However, the patient stopped applying the drops prematurely and returned at the end of this period because of a recurrence of mild conjunctival injection and the nummular corneal opacities. The opacities were less numerous and extensive at this time. Prednisolone 1% was again prescribed every two hours, and the symptoms and corneal lesions gradually subsided. Four weeks after the patient again began applying the corticosteroid drops, the cornea and conjunctivae were clear. The corticosteroids were tapered gradual-

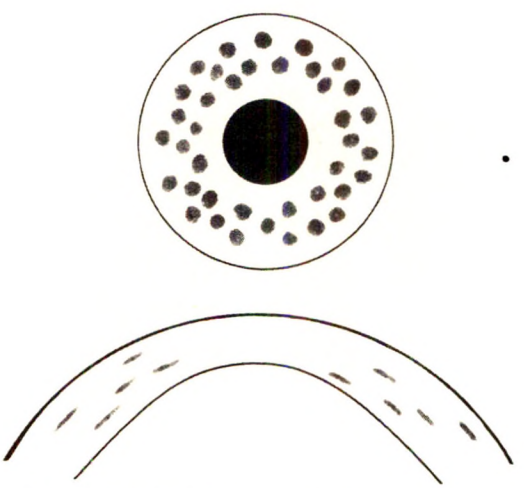

Figure (Pinnolis, McCulley, and Urman). Numerous nummular lesions in the peripheral cornea involving all levels of the stroma. The visual axis of the patient was spared.

ly over two more months, and discontinued without recurrence of signs or symptoms. Follow-up examination ten months after the patient had stopped taking all medicines showed a normal corrected visual acuity in both eyes. The conjunctivae were not inflamed. The cornea had no stromal opacities or superficial staining. In the superficial stroma, vessels extended from the corneoscleral limbus toward the visual axis 0.5 mm for 360 degrees in both eyes, but did not appear to be actively advancing. The anterior chambers showed no signs of inflammation in either eye. Results of dilated indirect ophthalmoscopic examination were normal.

Discussion

Payrau and Hoël[6] described a patient with presumed mononucleosis initially who had a follicular conjunctivitis and subsequently developed a superficial, epithelial, punctate keratitis associated with infectious mononucleosis. This patient developed a superficial, epithelial, punctate keratitis in the superotemporal quadrant of the left cornea, which progressed eventually to interstitial infiltrates and corneal edema involving only this one quadrant of the cornea. Finally, the patient developed interstitial vascularization of the cornea in this same quadrant. When the edema had cleared, a small piece of vegetable matter was noted to be lodged in the corneal stroma in this area, which was then removed. Their conclusion was that the virus had been directly injected into the corneal stroma via this vegetable matter.

The validity of the association of infectious mononucleosis and interstitial keratitis in this previous case[6] is questionable for the following reasons: (1) the only diagnostic test available was the heterophil antibody test, which is not highly specific for mononucleosis; (2) the authors did not eliminate any other possible causes of interstitial keratitis, especially viral causes, which might have affected this patient coincident with the mononucleosis; (3) the localized nature of the keratitis would indicate a local cause of the corneal lesion, such as the foreign body found in the involved quadrant.

In our case the patient had a bilateral, interstitial, nummular keratitis associated with a severe attack of infectious mononucleosis. The patient had ocular symptoms that seemed to be related to the course and severity of the illness; however, the corneas were first examined three months after the onset of the illness. This case of mononucleosis is unusual because the patient did not have a lymphocytosis. Lymphopenic infectious mononucleosis has been described and usually tends to be a more severe clinical illness when compared to typical cases of mononucleosis.[7] The diagnosis of infectious mononucleosis in our patient was confirmed with both a positive heterophil antibody test and a rising titer to the Epstein-Barr virus.

The differential diagnosis of nummular keratitits includes several entities that must be eliminated before attributing the process to the Epstein-Barr virus. Herpes simplex, herpes zoster, and epidemic keratoconjunctivitis caused by an adenovirus can cause a nummular, interstitial keratitis. Additionally, there is the nummular keratitis of Dimmer[8] and related processes described by Westhoff[9] and Laugraulet,[10] as well as a nummular keratitis associated with brucellosis.[11]

Our patient is unlikely to have Dimmer's keratitis, the related conditions, or brucellosis. He was not a farmer or land worker, and had no exposure to raw meat. The corneal opacities in these entities are larger, less numerous, located in the visual axis, and often unilateral. The lesions also typically develop a characteristic central depression as they resolve.

Herpes simplex or zoster keratitis is unlikely because our patient had bilateral lesions, normal corneal sensation, no epithelial defects, no anterior chamber reaction, and no rise in viral titers to herpes simplex. An adenovirus infection is unlikely because there was no titer rise

to adenovirus, and the lesions were not confined to the superficial stroma.

It therefore seems that the Epstein-Barr virus is the most likely cause of this keratitis. To the best of our knowledge this is the first well-documented case of infectious mononucleosis keratitis. Ophthalmologists faced with nummular keratitis, which often falls in the idiopathic category, should consider the Epstein-Barr virus as a possible cause. Infectious mononucleosis is often clinically asymptomatic, which would make it necessary to show a rising titer to the virus to establish the association.

Summary

A 16-year-old boy had a severe case of infectious mononucleosis with a rising titer to the Epstein-Barr virus. The patient had developed a nummular keratitis apparently associated with this illness. Because infectious mononucleosis or infection by the Epstein-Barr virus is often subclinical, and many cases of nummular keratitis have been classified as idiopathic in the past, a possible association between the two in such cases should be considered.

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TISSUE ADHESIVE ARRESTS STROMAL MELTING IN THE HUMAN CORNEA

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The use of cyanoacrylate adhesive in the management of corneal perforation has been well documented.[1] In the present series of cases early use of this topically applied cement has been used effectively to interrupt progressive corneal melting in various ulcerative disorders before anticipated perforation could occur.

SUBJECTS AND METHODS

Proper application of isobutyl 2-cyanoacrylate adhesive requires the magnification provided by the biomicroscope or the operating microscope. Depending on circumstances, the biomicroscope is generally adequate even for young patients (Case 1). Topical anesthetic is required and in some cases an eyelid speculum helps to ensure uninterrupted application and sufficient opportunity for the adhesive film to dry. The ulcer base is debrided with a Weckcel sponge or cotton-tipped applicator, and the circumferential epithelium is removed with a Bard-Parker blade or Kimura spatula to the basement membrane level for a width of at least 1 mm all around. Cultures may be taken from the debrided tissue. The Weckcel sponge ensures a dry field just before the application of cement. Cyanoacrylate adhesive is sparingly applied with the accessory applicator (Fig. 1) to ensure thin but even coverage of the prepared site, because with polymerization the adhesive film thickens somewhat and allowance for this must be made. Attention is paid to total coverage, to complete peripheral application to adjacent normal basement membrane, and to providing as thin a layer as possible so as to minimize discomfort and the tendency of the adhesive plaque to dislodge with eyelid action. When the cement has dried, a thin bandage contact lens (for example, Bausch and Lomb T-series) is placed over the treated cornea. Outpatient follow-up and appropriate adjunctive therapy (for example, antibiotics, collagenase inhibitors, and ascorbate) may be initiated. If the adhesive plaque becomes dislodged prematurely, it can be reapplied. It is beneficial for the cement to remain in place for six to eight weeks to allow

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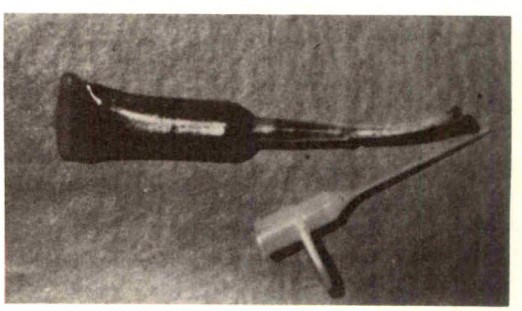

Fig. 1 (Fogle, Kenyon, and Foster). Cyanoacrylate tissue adhesive with accessory applicator (bottom).

healing. At that time, it can be removed and the bandage lens replaced to guard the surface if a sound epithelium has not regenerated.

The ten cases in this series (Table) represent various types of corneal surface disease, predominantly herpetic keratitis (Cases 1 to 3) and keratitis sicca (Cases 5 and 6), which often precede stromal melting. These conditions responded favorably to early application of cyanoacrylate adhesive with a bandage lens. Adjunctive therapies, such as topical antibiotics, collagenase inhibitors, corticosteroids, medroxyprogesterone acetate, and systemic ascorbate were used; conjunctival transplantation was per formed in one instance (Case 10). Such additional therapies were used only on the basis of individualized indications and careful observation. A favorable response was judged to be a mitigation or frank arrest of the acute melting process, and in all cases relative stability was gained without more invasive emergency measures.

Case Reports

Case 1—A 10-year-old boy developed recurring bilateral keratitis at age 2 years. The condition was diagnosed as stromal herpes. When initially examined in 1974, visual acuity was R.E.: 6/15 (20/50) and

TABLE

Summary of case reports

Case No., Age (yrs), Sex	Disease	Comment
1, 10, M	Herpes simplex	See Case Reports
2, 30, F	Herpes simplex, persistent epithelial defect	Corticosteroid "dependence"; stable after placement of adhesive and soft lens until addition of corticosteroid led to perforation
3, 66, F	Herpes zoster, possible herpes simplex	Melting began after scraping for calcium; stable vascular pannus developed under adhesive and soft lens in place for nine months
4, 40, F	Erythema multiforme (Stevens-Johnson syndrome	See Case Reports
5, 48, F	Rheumatoid arthritis, keratoconjunctivitis sicca	Central ulcer treated and adhesive and lens removed once stable; in one month, required repeat therapy and stabilized quickly
6, 69, F	Keratoconjunctivitis sicca	Medroxyprogesterone and soft lens failed to control central melting; improved in two weeks after adhesive and soft lens application
7, 72, F	Limbal melting in both eyes after cataract surgery	Bilateral application with adjunctive medroxyprogesterone; vascular scarring and intact epithelium developed under adhesive
8, 64, M	Healed perforation after *Pseudomonas* ulcer	Applied twice, promoted vascular scar, allowed keratoplasty later
9, 53, F	Radiation keratitis	Melting arrested at descemetocele
10, 40, M	Alkali burn, history of two penetrating keratoplasties	See Case Reports

Fig. 2 (Fogle, Kenyon, and Foster). Case 1 (herpes simplex). Initial appearance of acute central stromal melting with descemetocele.

L.E.: 6/18 (20/60). There were bilateral stromal opacities and stromal vascularization had occurred in the left eye. Two years later the patient developed an episode of metaherpetic keratitis in the left eye that required patching, hypertonic solutions, idoxuridine, and topical corticosteroids for resolution. This course was repeated seven months later. A year after this second course, a traumatic abrasion in the left eye did not respond to such conservative therapy. It quickly developed into a central descemetocele, suggesting inevitable perforation (Fig. 2). He easily tolerated the application of tissue adhesive at the slit lamp in the manner described previously (Fig. 3). A Bausch and Lomb T-series bandage lens was applied and systemic ascorbate sodium was prescribed. Superficial and deep vessels coursed into the cemented zone, and on removing the adhesive plaque after two months, it was noted that approximately one fourth of stromal thickness had returned. The reapplication of a bandage lens alone, with continued ascorbate sodium therapy, led to near restoration of full corneal thickness within one month. The central leukoma and associated vessels became less conspicuous during the following year, and the resulting visual acuity was 6/9 (20/30) in the treated eye (Fig. 3) .

Case 4—A 40-year-old woman had erythema multiforme of unknown cause in 1963. Marked keratinization of the tarsal conjunctivae developed, with superficial scarring in both eyes, and visual acuity of R.E.: 6/120 (10/200) and L.E.: 6/400 (3/200). No symblephara were present, and the eyes were not dry. Over the subsequent 15 years, 15 surgical procedures were performed, including mucous membrane grafts, conjunctival flaps, superficial keratectomies, lamellar keratoplasties, and four penetrating keratoplasties. The failures of the penetrating keratoplasties were caused by various ocular surface abnormalities, including recurrent erosion, persistent defects, trophic ulcers, and superficial vascularization. However, by using extended-wear soft contact lenses, the patient had visual acuity of R.E.: 6/9 (20/30) and L.E.: 6/12 (20/40) as recorded in July 1977. A year later, visual acuity was R.E.: 6/30 (20/100) and L.E.: 6/18 (20/60), as surface haze and vascularization

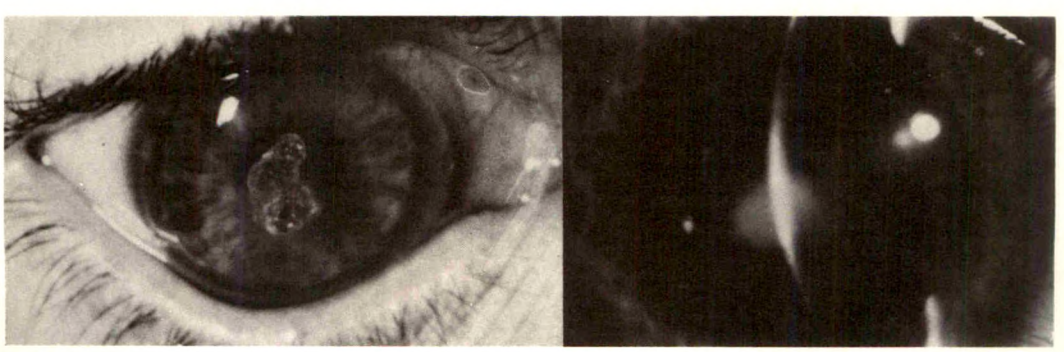

Fig. 3 (Fogle, Kenyon, and Foster). Case 1. Application of adhesive and bandage lens (left) is followed in one year by renewed stromal thickness with minimal scarring and vascularization (right).

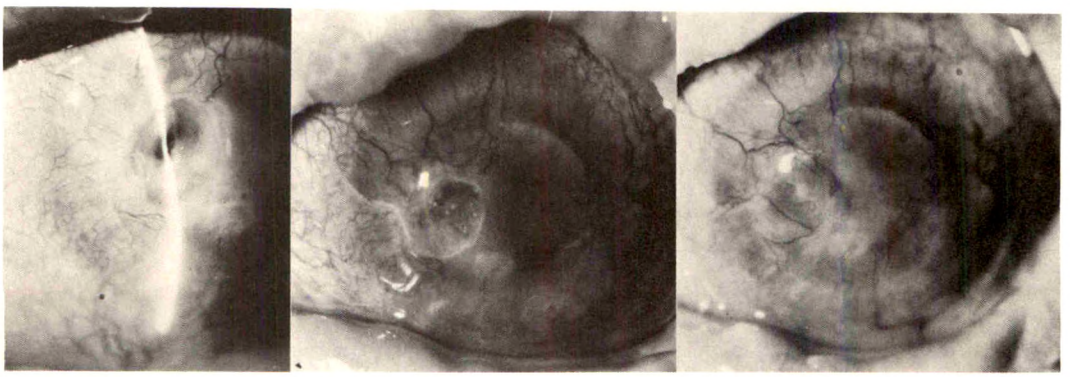

Fig. 4 (Fogle, Kenyon, and Foster). Case 4 (erythema multiforme). Left eye with descemetocele (left) treated with adhesive and a bandage lens (center). After three months, stromal integrity was restored and stabilized (right).

had continued quickly in the left eye. A 5-mm sterile trophic ulcer with 30% stromal melting had developed in the right eye, which was successfully treated with topical antibiotics and acetylcysteine, together with a bandage lens and systemic ascorbate sodium. Two weeks later, a 3-mm defect with 50% stromal melting developed in the left eye, and culture was positive for *Proteus*. The ulcer was managed with antibiotics and adhesive-bandage lens therapy as described previously. Topical corticosteroids were given. Within one week, however, the glue became dislodged, and a pinpoint leak within a descemetocele was observed (Fig. 4). This was managed with tissue adhesive applied under slit-lamp observation, and the patient's cornea gradually vascularized and thickened while he was receiving antibiotics and systemic ascorbate sodium. Two months later, the right eye, still receiving topical corticosteroids, developed a persistent epithelial defect, with stromal melting to a near descemetocele about 5 mm in diameter (Fig. 5). An adhesive-bandage lens was applied and the melting process was arrested. Tear samples were obtained from the melting surface of the right eye and from the quiescent surface of the left eye. The former sample revealed an abundance of polymorphonuclear neutrophils (Fig. 5), whereas the latter contained essentially no inflammatory cells. The cement remained in place on the right eye for four months, after which it dislodged spontaneously to reveal a nearly restored stroma that has remained stable for more than three months.

Case 10—A 40-year-old man received an alkali burn to the left eye in 1968. In 1976 he underwent a trabeculectomy and in 1977 had two keratoplasties in the injured eye. Three months after the second penetrating keratoplasty, a large epithelial defect deteriorated to a 3-mm descemetocele. When initially examined, visual acuity was R.E.: 6/4.5 (20/15) and L.E.: 6/1,200 (1/200). The left cornea showed an opaque, edematous grafted portion with the previ-

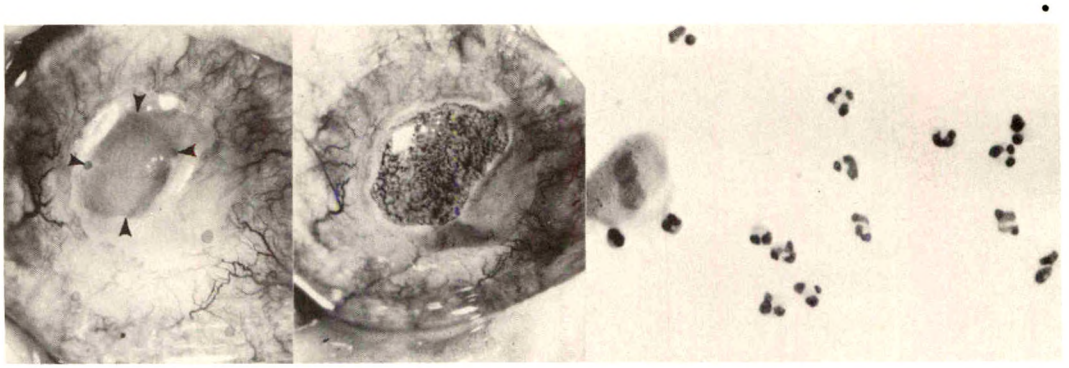

Fig. 5 (Fogle, Kenyon, and Foster). Case 4. Right eye with extensive central descemetocele (arrowheads) (left) treated with adhesive and a bandage lens (center). Tear samples disclosed numerous neutrophils (right) (Giemsa, × 1,000).

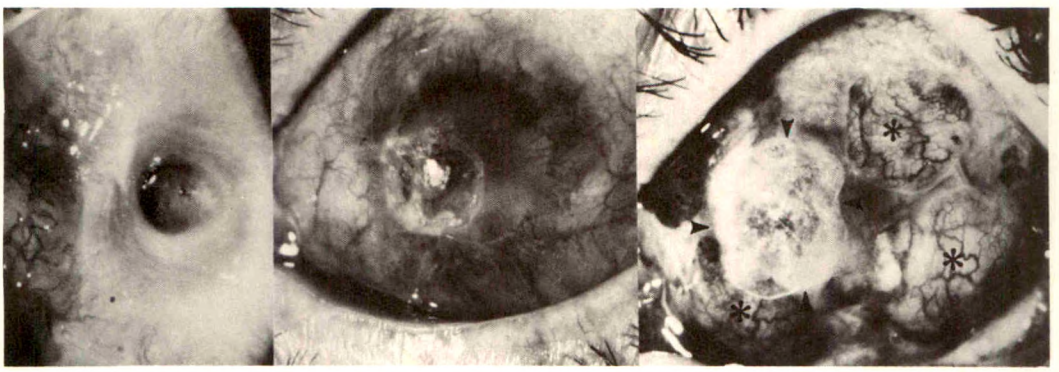

Fig. 6 (Fogle, Kenyon, and Foster). Case 10 (alkali burn). Central descemetocele (left) with immediate application of adhesive and a bandage lens (center). One week after conjunctival transplantation and adhesive reapplication (right). (Asterisks designate individual grafts of transplanted conjunctiva; arrowheads, tissue adhesive).

ously mentioned central descemetocele (Fig. 6). The anterior chamber appeared deep, and the tactile intraocular pressure was normal. The immediate application of tissue adhesive to the prepared ulcer and adjacent epithelial basement membrane, together with the placement of a bandage lens, was done in the face of imminent perforation. Several days later, a tectonic conjunctival transplant (similar to that recommended by Thoft[2]) was performed. The operation required the careful removal and subsequent replacement of the cement and bandage lens. After four months of healing, the adhesive became dislodged, and a pinpoint leak developed at the center of the incompletely healed descemetocele. Adhesive was then reapplied for a short time (Fig. 7), and subsequently a bandage lens alone was used to promote re-epithelialization. The eye became quiet and comfortable, with an intact surface and medically controlled intraocular pressure.

Bulbar conjunctiva, which was removed during the conjunctival transplant procedure, was examined by light microscopy. Many plasma cells and lymphocytes were noted, but there were few goblet cells (Fig. 8). The keratectomy specimen taken from the area of active corneal melting was also examined, and innumerable acute inflammatory cells, mainly polymorphonuclear neutrophils, were found (Fig. 8).

Discussion

Corneal melting, whatever its setting, is mediated in part by tissue collagenase.[3-11] There is no complete agreement about which cell or cells produce the collagenolytic enzymes, but most evidence has implicated the regenerating

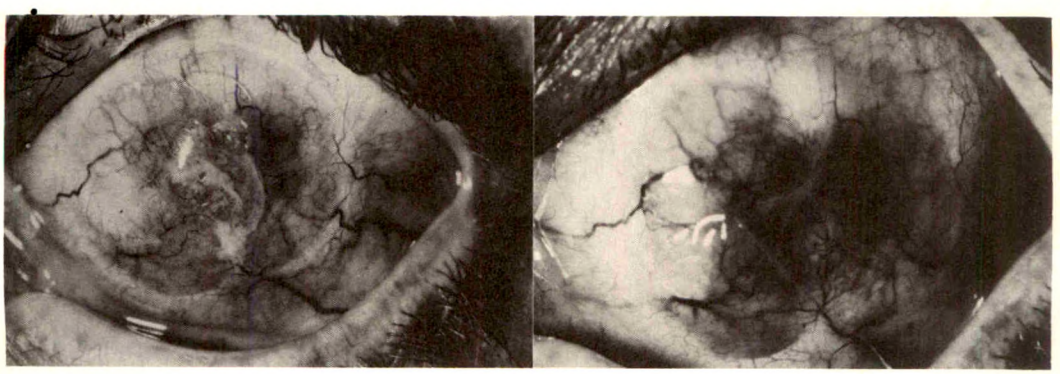

Fig. 7 (Fogle, Kenyon, and Foster). Case 10. A propitious "take" of the conjunctival grafts with adhesive and bandage lens still in place eight weeks postoperatively (left), and eventual resolution of the ulcerated zone with renewed surface five months postoperatively, after removal of adhesive plaque (right).

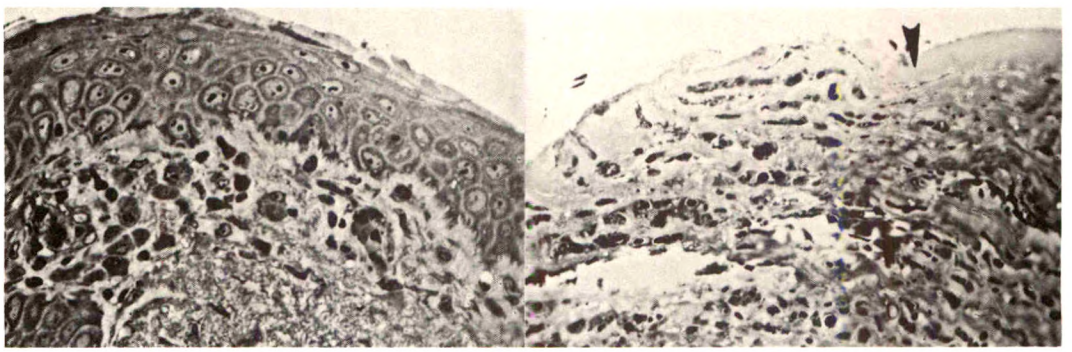

Fig. 8 (Fogle, Kenyon, and Foster). Case 10. Histopathologic section of conjunctival biopsy from nonulcerating region (left) shows absence of goblet cells and stromal infiltration with chronic inflammatory cells, predominantly plasma cells. Section taken from keratectomy material in region of active ulceration (right) discloses numerous polymorphonuclear neutrophils. Note termination of Bowman's layer at arrowhead (phase contrast, paraphenylenediamine, × 450).

epithelium adjacent to an ulcer and its interaction with subjacent keratocytes.[5,7]

Less attention has been directed toward the role of the polymorphonuclear neutrophil in corneal ulceration, despite evidence of potent collagenolytic and proteolytic activity by this inflammatory cell in certain experimental systems.[12-15] Recent experiments and observations have incriminated the polymorphonuclear neutrophil in human and experimental corneal ulcers.

Snip and Kenyon[16] did ultrastructural studies of melting human corneas obtained at keratoplasty for metaherpetic keratitis, stromal herpes, acute homograft reaction, and chemical injury. Stimulated polymorphonuclear neutrophils were present in all actively ulcerating eyes and these cells showed active phagocytosis and degranulation. By contrast, quiet descemetoceles were examined, and the presence of polymorphonuclear neutrophils was negligible.

A decade ago Dohlman and associates[17,18] suggested the "glued-on" contact lens as a plausible means of preventing regenerating epithelium from reaching a zone of damaged and naked stroma, and therefore preventing the presumably critical setting for collagenase production and progressive stromal melting. A recent investigation by Kenyon and associates[19-21] sought to re-evaluate this type of therapy in light of another probable reason for its apparent benefits: the inhibition of stromal infiltration by polymorphonuclear neutrophils. Using alkali-induced corneal melting in the rabbit model, a consistent circumstantial relationship was shown between active polymorphonuclear neutrophils and progressive stromal melting.[20] It was also shown that by removing epithelium from the alkali-burned area and applying a hard contact lens with a complete ring of cyanoacrylate adhesive, the stromal infiltration by polymorphonuclear neutrophils was greatly reduced and melting stopped. This interruption of the melting process was most successful when the contact lens was applied early in the course of melting, before overwhelming numbers of polymorphonuclear neutrophils had accumulated.

These same authors[21] evaluated the problem using direct ulcer coverage with cyanoacrylate adhesive at different stages of stromal melting in thermally damaged rabbit corneas.[19] Here the dried cement

served the same mechanical function as had the more arduously affixed hard contact lens, as melting was either prevented or arrested by direct adhesive application. Morphologic studies showed the ulcerating stromas of control corneas to be quite inflamed, largely with polymorphonuclear neutrophils, whereas corneas with cemented surfaces were essentially accellular in the affected stromal regions. This simpler barrier method of stabilizing stromal ulceration is analogous to our clinical technique.

Various studies suggest that chemotactic factors (such as a serum protease) may recruit polymorphonuclear neutrophils to a site of ulceration.[22,23] In the case of the cornea, this may be from corneoscleral limbus via stroma or from conjunctiva via tear fluid (Fig. 5). Robb and Kuwabara[24] showed the capability of polymorphonuclear neutrophils to arrive at a central corneal ulcer via the tear fluid, after their release from conjunctival vessels. Because polymorphonuclear neutrophils in tears seem to be the first to arrive in such a setting,[22] there may be some interaction between epithelium, keratocytes, or inflammatory cells, in any combination, causing a diffusible chemotactic factor that would elicit a stromal infiltration by limbal polymorphonuclear neutrophils. It is hypothesized that early superficial stromal invasion by acute inflammatory cells from tear fluid serves to start ulceration and to aid in the chemotactic recruitment of added cells via the stromal route. By either mode of access, a "glued-on" contact lens or adhesive application alone, as described in this report, should provide a barrier to both tear fluid and early regenerating epithelium and, thus, deter the invasion of stroma by polymorphonuclear neutrophils and prevent the accompanying damage.

Many investigators have sought to develop a reliable chemical or pharmacologic treatment that would prevent or combat the production or effect of collagenolytic enzymes in melting corneas as shown by published reports on acetylcysteine,[4,5] ascorbate,[25-27] ethylenediaminetetraacetic acid,[11] and medroxyprogesterone.[28] Although each of these agents has been shown to limit corneal melting in at least the experimental situation, there is still no dependable means of preventing progressive melting and perforation in an array of clinical settings. It is for this reason that the clinical technique described in this report was derived from the clinical and laboratory work of recent years, which implied a significant role for the polymorphonuclear neutrophil in stromal matrix degradation. In addition to the barrier effect described previously, a certain amount of structural support is undoubtedly given by the cement film, especially if care is taken to apply it fully to exposed circumferential basement membrane. If indicated, adjunctive therapies may be continued or initiated.

In an extremely torrid and widespread inflammatory ulceration, as may occur in Mooren's ulcer[29] or Wegener's granulomatosis, in all likelihood a preemptive accumulation of polymorphonuclear neutrophils, proteases, and collagenase may render adhesive application untimely and ineffective. However, in circumscribed corneal ulcerations that threaten to melt progressively and perforate, we suggest that the early application of tissue adhesive, in the simple manner described, may help to deter the course to perforation until reparative processes can stabilize the compromised cornea.

Summary

The direct early application of cyanoacrylate adhesive to a prepared ulcer bed and adjacent basement membrane, followed by placement of a bandage lens, gave good results in ten patients with corneal ulceration. The patients had ulceration with keratitis sicca, herpes

keratitis, and other surface diseases. Progressive melting was arrested in all cases, and concurrent adjunctive therapies were used as indicated. The technique is quick and simple.

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RELIEF OF PAIN BY SUBCUTANEOUS ELECTRICAL STIMULATION AFTER OCULAR SURGERY

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Pain after ocular surgery is a common occurrence. Medication with various mild analgesic drugs is the accepted, and usually, effective way to alleviate postoperative pain. However, ocular surgical procedures associated with highly increased intraocular pressure, such as cyclocryotherapy, circular buckling for retinal detachment, or evisceration, may cause severe and persistent pain that is not relieved even by the more potent analgesics. Postoperative administration of retrobulbar alcohol in seeing eyes has been recommended in order to prevent unnecessary suffering.[1]

Electrical stimulation of painful areas has been advocated as a new form of therapy in various pain syndromes,[2-4] postoperative pain being one of the conditions treated successfully by this method from the early stages of its use.[5-10] The electrical treatment was applied either through externally placed electrodes, that is, transcutaneous electrical stimulation, or by means of implanted subcutaneous wire electrodes, that is, subcutaneous electrical stimulation. In patients who had undergone thoracic,[5,6] abdominal,[7,8] orthopedic,[9] or gynecologic[10] operations, the application of transcutaneous electrical stimulation or subcutaneous electrical stimulation was successful in ameliorating postoperative pain. Some patients even preferred electrical stiumulation therapy instead of treatment with analgesic drugs.

In opthalmologic immediate postoperative pain relief, however, electrical stimulation has not been used. We present the results obtained with subcutaneous electrical stimulation applied to patients who had been subjected to various surgical ocular procedures.

SUBJECTS AND METHODS

Twenty-five patients (12 females and 13 males, aged 17 to 71 years) who underwent ocular surgery were treated by electrical stimulation for postoperative pain relief. Twenty-one patients received subcutaneous electrical stimulation by means of implanted steel wire electrodes. In four patients, who suffered from persistent late postoperative pain, transcutaneous electrical stimulation was administered by way of externally placed silicone rubber electrodes. The surgical procedures consisted of cyclocryopexy in 12 patients, cataract in six, retinal detachment in six, and vitrectomy in one patient (Table). In 19 of the 21 patients who received subcutaneous electrical stimulation, sterile wires were introduced in the area adjacent to the supraorbital and infraorbital nerves at the end of the surgical procedures and while the patient was still under local or general anesthesia (Figs. 1 and 2). The other two patients complained of severe pain in the eye three to 14 days after surgery and subcutaneous electrical stimulation was introduced at this late postoperative stage.

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TABLE

PERTINENT DATA OF THE PATIENTS AND RESULTS OF ELECTRICAL STIMULATION*

Patient No., Age (yrs), Sex	Surgical Treatment	Anesthesia	Type of ES	Duration (days)	Results	Remarks
1, 46, M	Retinal detachment	Local	SES	2	Very good	Reoperation
2, 48, F	Cataract	Local	SES	2	Very good	—
3, 64, M	Cataract	Local	SES	2	Good	—
4, 70, M	Vitrectomy	Local	SES	1	Good	—
5, 71, F	Retinal detachment	General	SES	2	Very good	Reoperation
6, 71, F	Retinal detachment	Local	SES	3	Very good	Reoperation
7, 63, M	Cataract	Local	SES	3	Very good	Allergic to drugs
8, 71, F	Cyclocryopexy	Local	SES	1	Very good	Retrobulbar alcohol block in previous surgery
9, 40, F	Cyclocryopexy	Local	SES	1	Good	—
10, 52, M	Cyclocryopexy	Local	SES	—	—	Reoperation; patient opposed—treatment interrupted
11, 58, F	Retinal detachment	General	SES	2	Good	Reoperation
12, 14, F	Cyclocryopexy	General	SES	1	Fair	Reoperation
13, 70, F	Cyclocryopexy	Local	SES	1	Good	—
14, 46, M	Cyclocryopexy	Local	SES	2	Very good	—
15, 65, M	Cyclocryopexy	Local	SES	1	Very good	—
16, 25, F	Cyclocryopexy	Local	SES	1	Very good	—
17, 53, F	Cyclocryopexy	Local	SES	1	Fair	Severe ischemic heart disease
18, 51, M	Cyclocryopexy	Local	SES	1	Good	
19, 61, F	Cyclocryopexy	General	SES	—	—	Patient opposed—treatment interrupted
20, 45, M	Retinal detachment	†	SES	2	Good	Reoperation
21, 70, M	Cataract	†	SES	1	No effect	Pain relieved by subsequent retrobulbar alcohol block
22, 65, F	Retinal detachment	†	TES	5	Good	—
23, 42, M	Retinal detachment	†	TES	7	Good	
24, 74, M	Cataract and bulbous keratopathy	†	TES	7	Good	—
25, 51, M	Cataract	†	TES	3	Fair	—

*ES designates electrical stimulation; SES, subcutaneous electrical stimulation; and TES, transcutaneous electrical stimulation.

†Treatment with ES was instituted in the late postoperative period.

Treatment was given immediately after surgery with a portable battery-operated nerve stimulator to which the electrode wires were attached. The apparatus has a frequency of 80 Hz, a pulse duration of 0.4 msec and generates asymmetric square pulses. It is also equipped with a second type of preset electrical stimulation (the modulation current output) (Fig. 3). When the modulation current is turned on, the duration of the pulse waves increases continually and gradually from 0.4 to 0.6 msec during a total period of 0.2 msec, after which it automatically reverts to the 0.4 msec pulse duration, to restart the whole cycle. This will result in an automatic average increase of the current intensity by approximately 25%. The basic initial electrical stimulation produces a delicate feeling of tingling and the modulation current is perceived as a pulsating type of

Fig. 1 (Ticho, Olshwang, and Magora). Patient with implanted wire electrodes in the area of the supraorbital and infraorbital nerves.

Fig. 2 (Ticho, Olshwang, and Magora). Patient connected to the nerve stimulator.

coarse vibration deep in the eye and its surrounding area. The intensity and type of current stimulation is adjusted by the patient himself during the period of treatment that lasts from one to three days, sometimes continuing around the clock. In the patients with late postoperative pain, electrical stimulation was continued and treatment lasted up to seven days.

Each patient was checked periodically throughout the course of treatment with regard to his general condition, analgesic needs, and stimulator performance.

Results

The effect of electrical stimulation was assessed according to the subjective feeling of pain of the patient and his need for analgesic drugs. The results were defined as follows: "very good" when the patient was free of pain and no drugs were required, "good" when pain was moderate and sedatives or mild analgesic drugs sufficed, and "fair" when the pain persisted despite electrical stimulation and analgesic medication, but the patient refused to interrupt the stimulation. In the 19 patients in whom treatment with subcutaneous electrical stimulation was started immediately upon termination of surgery, results were "very good" in nine, "good" in six, and "fair" in two patients. Two patients were apprehensive and refused electrical stimulation treatment after a short trial (Table). Of the six patients with late or chronic postoperative pain, the results were "good" in four, "fair" in one, and had no effect in the last patient. In seven patients who had undergone previous ocular surgery, subcutaneous electrical stimulation treatment compared favorably with earli-

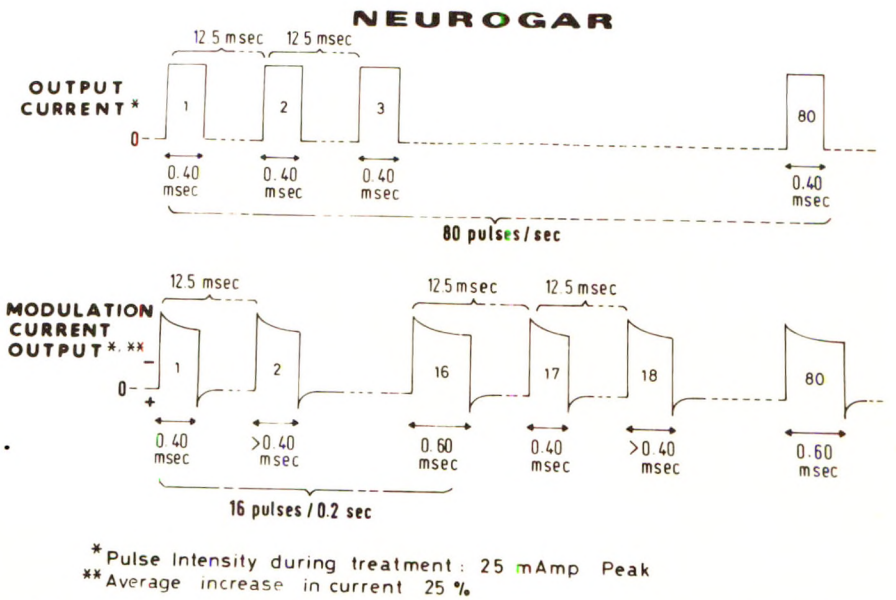

Fig. 3 (Ticho, Olshwang, and Magora). The current output of the electrical nerve stimulator.

er pain relief. One of the patients, who had received subcutaneous electrical stimulation postoperatively after previous ocular surgery, requested this mode of treatment after the surgical procedure.

Despite the continuous application of electrical stimulation, especially during the first 24 postoperative hours, the patients were able to move freely, because the implanted electrodes were well secured and bodily movement did not alter the electrical conductivity. However, in some instances, subcutaneous electrical stimulation was inadvertently interrupted because of sudden disconnection of the electrodes or exhaustion of the batteries. In these cases, pain often returned, but disappeared again after electrical stimulation had been re-established.

There were no complications associated with the electrical stimulation therapy such as skin burns, bleeding tendency, and the like. The electrode wires were removed easily upon completion of the treatment.

Discussion

Prolonged alleviation of pain was attributed by many investigators[11,12] to a peripheral physiologic effect caused by stimulation of the large fibers in the dorsal column in accordance with the "gate theory" put forward by Melzack and Wall.[13] Electrical stimulation is particularly suited for the treatment of postoperative ophthalmic pain as compared to other surgical procedures, because the circumscribed area of ocular pain is innervated mainly by two superficial nerves that afford easy access for therapy by stimulation. In addition to its electrical stimuli, electrical stimulation also exerts a mechanical effect, depending on the selection of the modulation current. This effect is particularly important after ocular surgery, because the patient is not allowed to massage, scratch, or apply pressure on the wound, in contrast to other types of surgery such as limb or abdominal operations. Although a placebo effect should not be excluded, Chapman,

Chen, and Bonica[14] have shown that the result of electrical stimulation treatment is not solely related to such a response. In the present series, direct placebo studies were not conducted; however, inadvertent interruption of the stimulation without the patient being aware of the break elicited pain sensations which, in all instances, were suppressed upon re-establishment of the stimulation. These observations strongly indicate that pain relief by means of electrical stimulation is the result of its physiologic effects.

Problems of electrical conductivity across the electrode skin interface often arise when externally placed electrodes are used. Localized concentration of current density and a spiking discharge causing unpleasant sensations may occur during sudden movement of the electrodes or changes in skin resistance caused by any other factor. In contrast, implanted electrodes are stable and bypass skin resistance; as a result, stimulation is uniform and pleasant, and current intensity necessarily minimal.

Insertion of the electrodes is a simple and painless procedure; it is performed under sterile conditions at the end of the operation while the patient is still anesthetized. Exact placement and maintenance of the electrodes near the supraorbital and infraorbital nerves is easily attained.

Pain after ocular surgery is, in general, not a major complaint. However, certain types of intervention or re-operation, together with the patient's personality, may render the early postoperative period difficult and extremely painful.

Treatment with electrical stimulation in a group of 25 patients completely abolished postoperative ophthalmic pain in nine patients and ameliorated the pain in 13. Intermittent or continuous application of electrical stimulation via subcutaneously implanted electrodes should be considered in the treatment of ocular pain in the immediate postoperative period in general and particularly in those surgical procedures in which postoperative pain is anticipated. Late postoperative ocular pain may be treated by either subcutaneous or transcutaneous electrical stimulation.

Summary

Electrical stimulation in the treatment of postoperative ophthalmologic pain was applied in 25 patients. In 21, stimulation was applied by means of subcutaneously implanted wires and in four patients the therapy was administered by externally placed electrodes. The subcutaneous electrodes were introduced near the supraorbital and infraorbital nerves at the end of the surgical procedures, and stimulation was immediately begun. Duration of treatment varied between one and three days.

The nerve stimulator is a portable, battery-operated apparatus. The implanted electrodes avoid skin resistance and are extremely stable, thus affording uniform current intensity that does not change during sudden movements. As a result, the stimuli are perceived as a pleasant sensation. Complete pain relief was attained in nine patients, and in 13 patients the pain was diminished. The therapy is appropriate and effective in postoperative ocular pain, because the pain is restricted to a limited area, innervated by superficial nerves that are easily accessible to electrical stimulation.

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MYDRIASIS FROM TOPICALLY ADMINISTERED PHENYLEPHRINE HCl POWDER

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Aqueous solutions of commercial mydriatic and cycloplegic drugs contain several chemicals. These include the principal drug, a buffer, one or more preservatives, and a stabilizer.[1] When one of these solutions, such as 10% phenylephrine HCl, is dropped into the conjunctival sac, a considerable amount of reflex blinking, tearing, irritation, and discomfort occurs. Several applications of 10% phenylephrine HCl drops over a period of at least 30 minutes are commonly used to produce mydriasis in patients. Many of our clinic patients who are older and who have heavily pigmented irides require five or more drops in each eye for mydriasis. Each drop contains about 70 mg of fluid, and the ten drops, or 700 mg of fluid, contain 70 mg of phenylephrine HCl.[2] We reduced the amount of phenylephrine HCl used in order to avoid the ocular irritation by placing phenylephrine HCl powder directly into the conjunctival sac. A single application of as little as 0.05 mg (50 μg) of the powdered drug was required to produce clinically useful mydriasis. This was accomplished without ocular irritation or reflex tearing. We report several methods of administering minute amounts of drugs to the eye.

MATERIAL AND METHODS

Phenylephrine HCl was powdered and microgram amounts of the drug were weighed on a Kahn Electro-balance Model M-10. The powder was transferred to a small folded section of waxed weighing paper. The paper was used to apply the drug to the lower fornix of one eye. Although small amounts were used, it was possible to see the white fluffy powdered drug land in the lower fornix. The data were recorded only when the powder administered to the eye was observed. With the doses of 25, 50, and 80 μg, consistent delivery of drug was possible; however, with the 5- and 10-μg doses, the application had to be repeated in three of the 20 subjects the next day. Ten subjects received the 5-μg dose and ten received 10 μg. All were whites, ranging in age from 21 to 54 years. They were instructed to blink several times and then to resume normal activity. One observer measured pupil diameters in a well-lighted room under double-masked conditions.

Three substances were investigated to evaluate the feasibility of a diluent for the phenylephrine HCl powder. Samples of sucrose, dextrose, and alpha-methylcellulose 1,500 centipoise, were all ground into fine powders. Amounts of 250 and 500 μg of each substance were administered to the lower fornix of each of five subjects.

Various devices were designed and experimented with in an attempt to develop a method to consistently air-deliver a given amount of powdered phenylephrine HCl, pilocarpine HCl, and fluorescein. Mixtures of sucrose plus fluorescein were prepared to test the effectiveness of drug blown from a device into a beaker containing 50 ml of water. A standard solution was prepared by dissolving 250 μg of fluorescein in 50 ml of water. Ten at-

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tempts gave a mean of 250 μg with an error of ±8.0%.

Results

Phenylephrine HCl powder in amounts of 5, 10, 25, 50, and 80 μg was administered to the conjunctival sac of each of ten volunteers. No ocular irritation was noticed. The amount of mydriasis followed a dose-response relationship; near-maximum mydriasis with 50 μg of powder. Mydriasis useful for ocular examination was produced with a single application of 50 μg of powder (Fig. 1). The onset of mydriasis from a single application of 50 μg of phenylephrine HCl to ten subjects was similar to that produced after three applications of 10% phenylephrine HCl eyedrops given at five-minute intervals to ten subjects (Fig. 2). After the use of 10% phenylephrine HCl eyedrops, a rebound hyperemia of conjunctival blood vessels and ocular itching developed about eight hours later in ten subjects. A similar effect was noticed in four subjects after the application of 80 μg of the powder. All subjects gave a detectable mydriasis to the 5-μg dose of powder under double-masked conditions. A dose of less than 5 μg was too small to weigh accurately and administer to the conjunctival sac, although two subjects with blue irides gave detectable mydriasis after receiving an estimated 2 μg of the powder.

Administration of powdered drugs to the conjunctival sac was attempted with a puff of air. The approach used was to air-suspend the drug with a carrier chemical and to administer a fraction of the suspended powder. Chemicals used as the carrier were alpha-methylcellulose, dextrose, and sucrose. As little as 50 μg of alpha-methylcellulose powder produced ocular irritation, dextrose produced minimal irritation, and sucrose produced no irritation. Fifty μg of phenylephrine HCl was mixed with 150 μg of sucrose on a piece of paper. This was blown into the eye with a rubber ear bulb. In three subjects maximum mydriasis was produced with a minimum amount of transient stinging and there was no evidence of excess tearing.

A noncontact tonometer ("puff-tonometer") was used to produce a con-

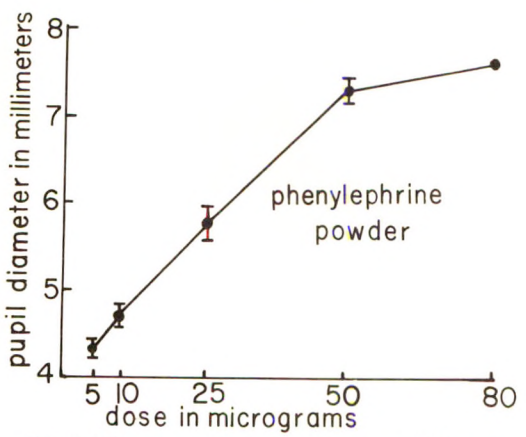

Fig. 1 (Thornton and Hanna). Dose-pupil diameter response curve for phenylephrine HCl powder. Subjects received from 5 to 80 μg of phenylephrine HCl in one eye. White subjects were used; the mean and standard error of the mean (bracket) were given where N=8, except for 10-μg dose where N=10.

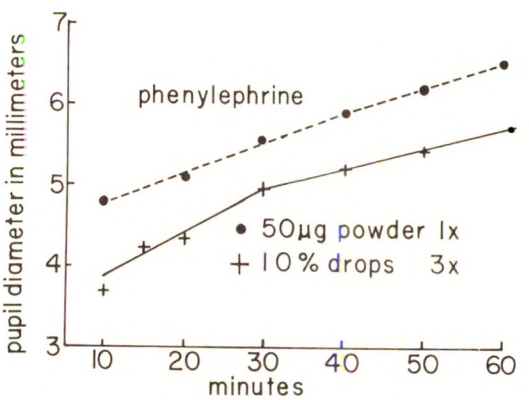

Fig. 2 (Thornton and Hanna). Time-pupil diameter response curve determined from those subjects receiving three sets of 10% phenylephrine HCl drops at five-minute intervals (bottom curve measurement started after last set of drops), and ten subjects receiving a single application of 50 μg of powder (bottom curve).

sistent puff of air. The tip of the air outlet was capped with a gum rubber serum bottle cap. Two small holes were made into the cap and a microhematocrit tube, which contained powdered drugs, was inserted into one. A curved piece of glass tubing was inserted into the second hole. Glass tubings with various internal diameters were used to reduce the air pressure delivered to the hematocrit tube. The pressure of the tonometer was adjusted in this way so that the puff of air would gently blow powdered drug from the hematocrit tube for a distance of about four inches. Powdered fluorescein (250 μg) was mixed with an equal weight of pulverized sucrose and the hematocrit tube pushed to a marked distance in the powder. The powdered fluorescein and sucrose were blown from the hematocrit tube into 50 ml of water. The concentration for fluorescein in the water was compared with a standard solution of 50 ml of water containing 250 μg of fluorescein under ultraviolet light. The hematocrit tube was calibrated to administer 250 μg of fluorescein and 250 μg of sucrose mixture. In ten attempts the error was ±8.0%. The same amount of powdered fluorescein and sucrose was blown into the eyes of ten subjects. In each case the pattern of fluorescein staining was centered on the cornea and extended around the conjunctiva and eyelids, but not on the rest of the face.

Several hand-held models were manufactured to use a reservoir that held powdered sucrose and drug. In one model a small receptacle at the bottom of the reservoir was calibrated to hold approximately 250 μg of the mixture. By rotating the receptacle, air could be used to blow the powdered mixture to the eye. However, after several rotations the powder tended to cake in the receptacle. The second model also made use of a reservoir. This reservoir contained an air inlet at the bottom and outlet at the top. When air from the noncontact tonometer was blown into the reservoir, the powder became air-suspended and some exited via a needle outlet (Fig. 3). It was necessary to pass the air through anhydrous calcium sulfate to remove moisture, otherwise the powder would not air-suspend after about 20 attempts. The administration rate of 250 μg of fluorescein and 250 μg of sucrose using this model in ten attempts was ±5.7%. A mixture of 150 μg of sucrose and 50 μg of phenylephrine HCl was blown into the eye of eight subjects and near-maximum mydriasis was produced in each eye at one hour. Although there was no ocular irritation produced, there was an unpleasant sensation caused by having a powder gently blown into the eye.

Twenty-five micrograms of pilocarpine HCl dusted into the eyes of seven subjects produced marked miosis (pupil size of less than 2 mm in diameter) in 30 minutes after a single application. The pilocarpine HCl application produced no immediate irritation or reflex tearing. However, conjunctival blood vessel vasodilation did occur, and this was accompanied by some ocular irritation until the vasodilation disappeared.

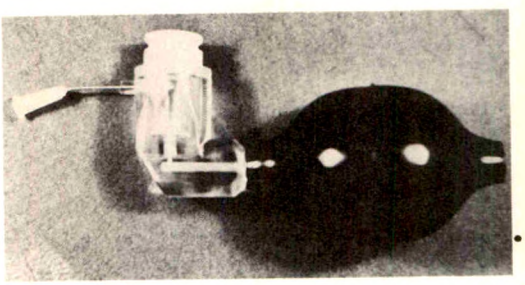

Fig. 3 (Thornton and Hanna). Apparatus used to administer powdered drug. Air was provided by the rubber bulb or a tubing from noncontact tonometer. An opening at the bottom directs the air upward through a reservoir containing suspended finely powdered sucrose and drug. A removable cap permits loading the reservoir and the amount of drug instilled is governed by the pressure, the duration of the air pressure, and the outlet needle gauge.

Discussion

Although each drop administered to the eye contains about 70 μl of liquid,[3] the amount reaching the eye can vary widely. In our clinic the older subjects with heavily pigmented irides often require at least five drops of 10% phenylephrine HCl to each eye over a period of an hour. This is about 7 mg of drug per drop and 70 mg per subject, or on the average of 1 mg/kg of body weight of phenylephrine HCl. Much of the medication passes from the surface of the eye through the punctum and into the nasal mucosa for systemic absorption.[4] An intravenous infusion of 1 mg/kg of body weight of phenylephrine HCl over several minutes can lead to a temporary increase in blood pressure in the dog.[5] The use of eyedrops of 10% phenylephrine HCl could lead to hypertensive episodes in some patients.[6,7]

It is not necessary to use 70-μl drops of 10% phenylephrine HCl to produce mydriasis in patients because 5-μl eyedrops can produce the same degree of mydriasis.[3] Conversely, 70-μl eyedrops of 1% phenylephrine HCl can be used[3] or the use of a single application of 5 to 10 μl of 10% phenylephrine HCl in ointment.[1,8] A single application of 5 μl of 10% phenylephrine HCl in ointment would deliver only 0.5 mg or 500 μg of the drug. In the first experiment we considered 125 μg of powdered phenylephrine HCl to be below the effective amount of drug. As a result, in four volunteers a maximum mydriasis was produced that lasted for more than five hours.

The single application of 50 μg of powdered phenylephrine HCl to the conjunctival sac produced a mydriasis as readily as did several applications of 10% phenylephrine HCl eyedrops. One difference between these two preparations was the lack of ocular irritation and reflex tearing with the powder. This may be because the 50 μg of powder, when mixed with about 7 μl of tear film, gives a little less than a 1% solution of drug. A 1% solution of this drug has produced minimum ocular irritation and reflex tearing.[3]

The minimum amount of powdered phenylephrine HCl required to produce detectable mydriasis in several blue-eyed subjects was less than 5 μg. This is less drug than is present in nonmydriatic vasoconstrictor eyedrops containing 0.08 to 0.2% phenylephrine HCl in which each eyedrop contains 56 to 140 μg of drug. Possibly when these eyedrops are allowed to dry on the container or finger and then touched to the eye, mydriasis could result. Similarly, Alani[9] allowed 0.5% tropicamide eyedrops to dry onto the tip of a rod and then the rod was applied to the conjunctiva with a subsequent mydriasis and cycloplegia.

The administration of powdered drug to the eye has the advantage of instilling the active drug in the absence of buffer, stabilizer, and preservative that are required for eyedrops.[10] The powder is stable and can be kept sterile. The problem of administering microgram amounts of powdered drug to the eye can be appreciated by noting that the average weight on one crystal of fine table salt is 100 μg. To administer microgram amounts of phenylephrine HCl, pilocarpine HCl, or fluorescein to the eye, powdered sucrose was added to increase the bulk being administered. Although it was possible to blow the required microgram amounts of drug along with the sucrose carrier into the eye without ocular irritation, this method of instillation does not seem satisfactory to us. Blowing even small amounts of powder into the eye by using a gentle flow of air resulted in an unpleasant sensation.

These studies suggest that the amount of drug required to produce a therapeutic effect is much less than currently being administered. Powdered drug uses

the tears to supply the vehicle. Because the amount of powder required is generally minute, the problem of ocular irritation can be avoided. In some instances, such as where the production of tears is reduced, the use of the powder may not be desired. A further problem is the general lack of availability of powdered drug. Phenylephrine HCl is available as a pure substance from several sources. This powder is white and fluffy and is readily weighed out and administered even in microgram amounts. Other powdered drugs, such as fluorescein or pilocarpine HCl, are more dense than phenylephrine HCl and are not readily administered in amounts of several micrograms.

Summary

Microgram amounts of finely powdered phenylephrine HCl were administered to the conjunctiva of volunteers. A dose-response curve for white subjects showed a threshold mydriasis of less than 5 μg and a clinically useful mydriasis was obtained with one application of 50 μg. The time-response curve for the one time use of 50 μg of the powder was equivalent to giving three applications of 10% phenylephrine HCl drops. Twenty-five micrograms of pilocarpine HCl powder produced marked miosis. We investigated methods to deliver nonirritating microgram amounts of powdered phenylephrine HCl, pilocarpine HCl, and fluorescein.

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ABNORMAL BRAIN STEM AUDITORY-EVOKED POTENTIALS IN STILLING-TÜRK-DUANE RETRACTION SYNDROME

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The Stilling-Türk-Duane retraction syndrome consists of severe limitation of abduction, slight limitation of adduction, and retraction of the globe with narrowing of the palpebral fissure when adduction is attempted.[1] Elevation or depression of the globe in adduction may also occur. The syndrome is seen more commonly in women than in men, and the left eye is affected more frequently than the right eye.[2] The condition is bilateral in approximately 20% of the cases.[3]

There has been considerable speculation concerning the cause of the retraction syndrome. Early studies favored structural theories, such as a posterior insertion of the medial rectus muscle or an inelastic lateral rectus muscle.[4] With the advent of electromyography, investigators discovered an innervational disturbance resulting in contraction of the lateral rectus muscle instead of relaxation when the medial rectus muscle contracts. Breinin[5] first described this anomalous simultaneous contraction and believed that it was caused by an abnormally sensitive stretch reflex in the lateral rectus muscle. Blodi, Van Allen, and Yarbrough[6] disproved this theory by showing contraction in an unstretched detached lateral rectus muscle.

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This simultaneous contraction in the Stilling-Türk-Duane syndrome could be caused either by a supranuclear brain stem abnormality or by an anomalous innervation of the lateral rectus muscle by the oculomotor nerve.[6,7] Brain stem auditory-evoked potentials are valuable in detecting brain stem disorders in humans.[8] We describe herein the brain stem auditory-evoked potentials in 14 patients with the retraction syndrome and how this technique implicates a supranuclear site for this disorder.

MATERIAL AND METHODS

We tested 14 patients who had the Stilling-Türk-Duane retraction syndrome (Table 1). Six were male and eight were female. In three patients, the right eye was affected and in eight patients, the left eye was affected. Three patients had bilateral involvement. Thirteen of 14 had normal audiograms. Patient 3 had the only abnormal audiogram and this was abnormal for high frequency. Two patients had associated syndromes. Patient 3 had Goldenhar's syndrome and Patient 8 had the Klippel-Feil syndrome. All patients tested were older than age 6 years.

We performed brain stem auditory-evoked potentials on all 14 patients. Each subject listened to clicks generated by 0.1-msec^2 waves with alternating polarity to each ear separately at ten per second. The clicks were 60 dB above the subject's hearing threshold. We recorded the brain stem auditory-evoked potential from electrodes placed at C_z and the ipsilateral ear lobe. Each trial consisted of averaging 2,048 click responses. At least two trials were performed for each

TABLE 1

PATIENT CHARACTERISTICS*

Patient No.	Sex	Affected Eye	Audiogram	Associated Signs
1	F	L.E.	N	N
2	F	L.E.	N	Goldenhar's
3	M	R.E.	Abnormal	N
4	F	L.E.	N	N
5	F	Both eyes	N	N
6	M	L.E.	N	N
7	M	Both eyes	N	N
8	M	L.E.	N	Klippel-Feil
9	F	R.E.	N	N
10	F	L.E.	N	N
11	M	L.E.	N	N
12	F	Both eyes	N	N
13	F	L.E.	N	N
14	M	R.E.	N	N

*N designates normal.

ear. Table 2 lists normative latency values for brain stem autitory-evoked potentials at our laboratory. These normal values are for patients older than age 6 years.

RESULTS

Tables 3 and 4 list the latency measurements of the brain stem auditory-evoked potentials of the right ear while stimulated and the left ear while stimulated. We noted no abnormalities in Waves I, II, and IV-VII. These waves showed no significant difference from normative values ($P \leq .05$).

TABLE 2

NORMATIVE LATENCY VALUES FOR BRAIN STEM AUDITORY-EVOKED POTENTIALS

Wave	Mean Latency (msec)	S.D. (msec)
I	1.5	.3
II	2.6	.4
III	3.7	.3
IV	5.1	.4
V	5.8	.3
VI	7.2	.4
VII	9.1	.4

There was, however, increased latency in Wave III. Table 5 lists the latency measurements of the right and left ears while stimulated in Wave III together with the patient's affected eye. In nine of the 14 patients, there was a significantly increased latency in Wave III ipsilateral to the affected eye ($P \leq .05$). Two of these nine cases were bilateral and in these two cases, there were increased latencies of Wave III bilaterally ($P \leq .05$).

DISCUSSION

Jewett, Romano, and Williston[9] were the first to describe a technique for recording auditory-evoked brain stem potentials in humans. A subject listens to repetitive click stimuli through earphones. Electrodes on the subject's scalp pick up the electrical response generated by the stimuli. The brain stem auditory-evoked potential is small in comparison to background brain electrical activity. It is therefore necessary to deliver over 2,000 click stimuli and to use an averaging computer to extract out the brain stem auditory-evoked potential.

TABLE 3

LATENCY MEASUREMENTS OF BRAIN STEM AUDITORY-EVOKED POTENTIALS WHEN RIGHT EAR IS STIMULATED

Patient No.	Wave (msec)						
	I	II	III	IV	V	VI	VII
1	1.6	2.7	4.0	5.1	5.8	7.6	9.3
2	1.5	2.6	4.0	5.2	5.9	7.6	9.3
3	1.9	3.2	4.4	5.4	6.1	7.7	9.4
4	1.5	2.7	3.9	5.0	5.7	7.6	9.1
5	1.5	2.5	4.3	5.2	5.8	7.5	9.1
6	1.6	3.0	4.1	5.1	5.7	7.6	9.2
7	1.4	2.7	4.5	5.3	6.0	7.2	9.1
8	1.6	2.7	3.8	5.0	5.7	7.1	9.0
9	1.5	2.6	4.2	5.0	5.8	7.4	9.2
10	1.6	2.8	3.8	4.9	5.6	7.1	9.0
11	1.6	2.5	3.7	4.8	5.6	7.2	9.1
12	1.6	2.7	4.2	5.1	5.9	7.4	9.3
13	1.5	2.6	4.0	5.0	6.1	7.7	9.4
14	1.4	2.5	4.3	5.2	6.0	7.6	9.4

The response generated by this technique consists of seven waves spaced over 10 msec. Jewett and Williston[10] labeled these waves sequentially with Roman numerals. Studies in cats indicate that the generators of Waves I-V are the acoustic nerve, cochlear nuclei, superior olivary complexes, lateral lemniscus, and inferior colliculi, respectively.[11,12]

Chiappa, Gladstone, and Young[13] studied the brain stem auditory-evoked potentials in 50 normal human subjects. They provided normative values for absolute latency measurements of the waves, interwave intervals, and wave amplitudes. The normative values for our laboratory are similar to those of Chiappa, Gladstone, and Young. With these

TABLE 4

LATENCY MEASUREMENTS OF BRAIN STEM AUDITORY-EVOKED POTENTIAL WHEN LEFT EAR IS STIMULATED

Patient No.	Wave (msec)						
	I	II	III	IV	V	VI	VII
1	1.5	2.6	4.4	5.2	5.9	7.4	9.1
2	1.6	2.6	4.3	5.1	5.9	7.4	9.0
3	1.8	3.3	3.8	5.0	6.0	7.5	9.2
4	1.5	2.6	4.3	5.1	5.9	7.3	9.1
5	1.6	2.5	4.4	5.2	6.1	7.4	9.0
6	1.6	3.0	4.2	5.2	6.1	7.4	9.0
7	1.4	2.7	4.3	5.1	5.9	7.3	9.1
8	1.5	2.7	4.4	5.2	6.1	7.4	9.1
9	1.6	2.6	3.8	5.0	6.1	7.4	9.0
10	1.5	2.7	4.2	5.1	5.9	7.2	9.1
11	1.6	2.5	3.7	4.9	6.0	7.4	9.0
12	1.6	2.7	3.9	5.0	5.9	7.2	9.1
13	1.4	2.6	4.3	5.1	5.9	7.1	8.9
14	1.3	2.4	3.8	5.0	6.0	7.1	9.4

TABLE 5

WAVE III LATENCY COMPARISONS

Patient No.	Affected Eye	Right Ear (msec)	Left Ear (msec)
1	L.E.	4.0	4.4*
2	L.E.	4.0	4.3*
3	R.E.	4.4*	3.8
4	L.E.	3.9	4.3*
5	Both eyes	4.3*	4.4*
6	L.E.	4.1	4.2
7	Both eyes	4.5*	4.3*
8	L.E.	3.8	4.4*
9	R.E.	4.2	3.8
10	L.E.	3.8	4.2
11	L.E.	3.7	3.7
12	Both eyes	4.2	3.9
13	L.E.	4.0	4.3*
14	R.E.	4.3*	3.8

*Designates significantly increased latency.

normative values, it is possible to recognize selective changes in the various components of the brain stem auditory-evoked potential. These changes provide anatomic localization of lesions.

The brain stem auditory-evoked potential has proven useful in a number of neurologic diseases involving the brain stem. They include: (1) detecting demyelination, (2) localizing neoplastic and vascular lesions, (3) monitoring the evolution and response to therapy of tumors, contusions, demyelination, and inflammatory processes, (4) differentiating metabolic from structural causes of coma, and (5) confirming brain death.[8,14-16]

Nine of our 14 patients showed increased latencies in Wave III of the brain stem auditory-evoked potential. The superior olivary complex in the pons generates this wave. We believe that the increased latency of Wave III in nine of our patients implicates a pontine disturbance as the cause of the Stilling-Türk-Duane syndrome in these patients. In the other five patients, four had moderately increased latencies, and one was clearly normal. Burian and von Noorden[1] emphasize that several causal factors may be involved in the retraction syndrome. Our patients with normal brain stem auditory-evoked potentials probably represent cases in which non-brain-stem mechanisms are responsible for the production of the retraction syndrome.

SUMMARY

We performed brain stem auditory-evoked potentials on 14 patients who had the Stilling-Türk-Duane retraction syndrome. Nine of the 14 had an increased latency in Wave III, implicating a pontine anomaly as the cause of the retraction syndrome in these patients.

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EXTRAOCULAR MUSCLE-TENDON TRANSFER WITH SCLERAL AUGMENTATION

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Extraocular muscle-tendon transfer, first described by Hummelsheim,[1] and used in several modifications, is now an accepted surgical procedure.[2] The usual indication for an extraocular muscle-tendon transfer is strabismus caused by one or more paralyzed or absent rectus muscles. Two requirements for a successful extraocular muscle-tendon transfer are: (1) one or more extraocular muscles capable of contracting, and (2) unrestricted passive ductions. The second requirement makes it necessary to recess the antagonist of the nonfunctioning muscle when the antagonist becomes contracted as it often does in long-standing paralytic strabismus.

When recession of the antagonist is necessary, our choice for extraocular muscle-tendon transfer is the rectus muscle union described by Jensen.[3] However, if there is no need to recess the antagonist, we prefer to use the full tendon transfer where rectus muscles are reattached to sclera adjacent to the paretic muscle. For example, the superior and inferior rectus muscles may be reattached to sclera adjacent to the insertion of a paretic medial rectus muscle. This may also be done in the case of an absent muscle provided there is no need to recess the antagonist of the missing muscle.

The reason for using different transfer procedures is to preserve an anterior ciliary artery in at least one muscle in order to reduce the likelihood of anterior segment ischemic changes.

A special problem occurs in rare cases where strabismus is caused by an absent rectus muscle and where recession of the antagonist is also required. In this type of case there is no muscle present to complete the rectus muscle union.[3] However, a full tendon transfer combined with recession of the antagonist would mean that all anterior ciliary arteries would be cut, thereby increasing the possibility of anterior segment ischemia. We describe a previously unreported technique for extraocular muscle transfer in cases where absence of a rectus muscle is combined with restriction of the antagonist.

MATERIAL AND METHODS

A thin strip of sclera measuring approximately 1.5 mm wide by 100 mm long is prepared from bank sclera that has been preserved in glycerin (Fig. 1).[4] The scleral strip may be reinforced with 4-0 Prolene suture woven through at 4.0-mm intervals. The middle of the scleral strip is sutured to the patient's sclera at or just posterior to the usual anatomic insertional site of the missing rectus muscle by using 5-0 Merseline suture. The ends of the scleral strip are passed through the adjacent rectus muscles that have been split longitudinally as is done in Jensen's rectus muscle union. The free ends of the scleral strip are then pulled toward each other over the site of the scleral attachment until the eye is in

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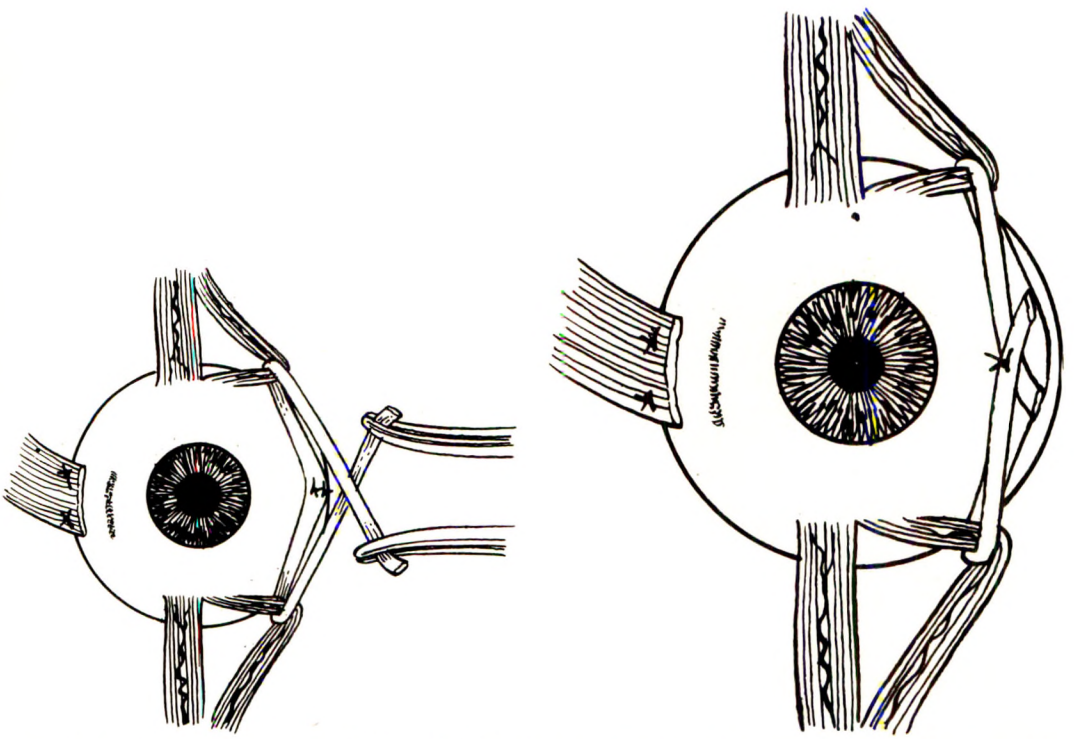

Fig. 1 (Helveston, Merriam, and Ellis). Left, Preserved sclera sutured to host sclera 6.0 mm from the corneoscleral limbus and placed around nasal half of superior and inferior rectus muscle. Right, Free ends of scleral strip sutured to each other with eye in slightly adducted position.

a slightly overcorrected alignment. The scleral strip is sutured to itself and the Prolene suture is tied. This procedure was done on two patients who had a long-standing large-angle exodeviation because of an absent medial rectus muscle.

Case reports

Case 1—A 50-year-old woman had had surgery performed for esotropia at age 5 years. Immediately after the operation, a large exotropia occurred. At age 32 years she had a second procedure that did not alter the exodeviation. All surgery was done on the left eye, but no details were available.

Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/120 (20/400) and a left exotropia of approximately 90 prism diopters was present (Fig. 2, top left). The left eye could not adduct to the midline. Adduction saccadic velocity of this eye was reduced and attempts at adduction produced no change in intraocular pressure.

At surgery, marked resistance to passive adduction of the left eye was noted. Dissection in the area of the left lateral rectus muscle showed extensive scar tissue with the left lateral rectus muscle attached to sclera 15 mm posterior to the corneoscleral limbus. When this muscle was dissected from the globe, the left eye could be passively adducted freely. Exploration of the medial side of the globe showed only fibrous tissue. The medial rectus muscle could not be found.

At this point, a scleral augmented rectus muscle union was performed as described previously. The lateral rectus muscle was reattached to sclera at the point where it had been detached from the globe, but the muscle was allowed to lag posteriorly, causing a recession to a point approximately 20 mm from the corneoscleral limbus.

Postoperatively, the patient had an exotropia of approximately 25 prism diopters (Fig. 2, top right). Because of a persistent delle at the nasal corneoscleral limbus caused by redundant conjunctiva, a recession of nasal conjunctiva was carried out two months later under local anesthesia. Six months after the first surgical procedure done by us, the patient maintained an alignment of 25 prism diopters of exotropia in the primary position with adduction approximately 10 degrees beyond the midline and there was no evidence of corneal drying (Fig. 2, bottom left).

Case 2—A 49-year-old woman had had a right exotropia since birth. According to the patient, surgery was done on the right eye when she was age

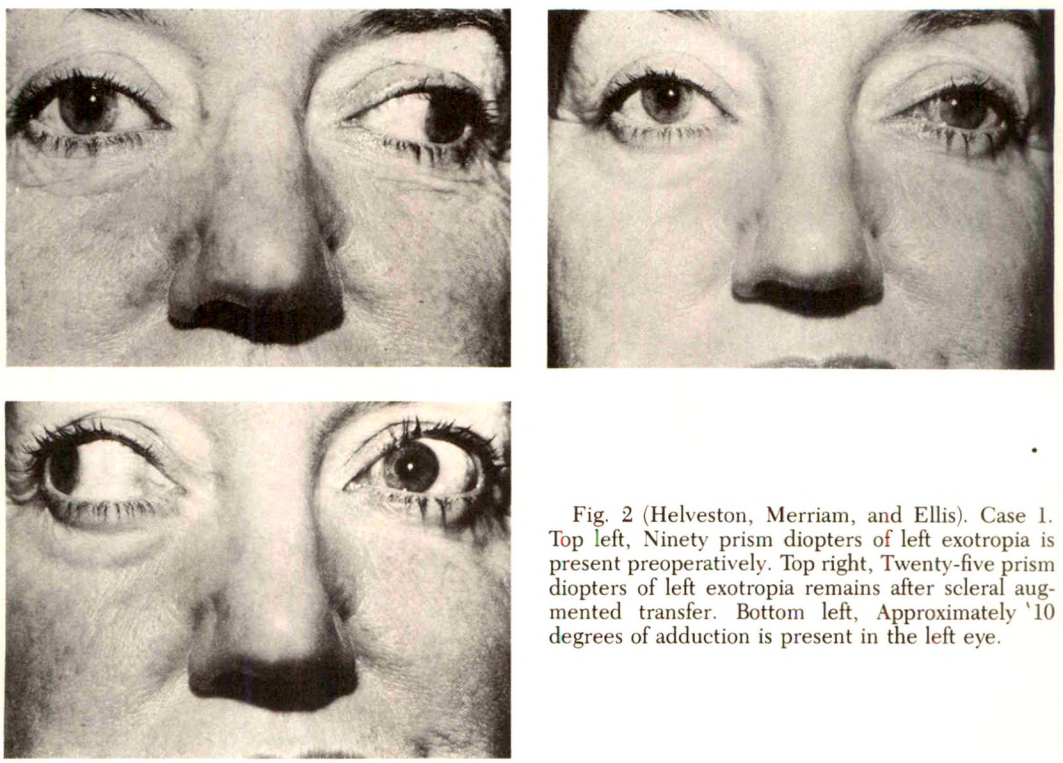

Fig. 2 (Helveston, Merriam, and Ellis). Case 1. Top left, Ninety prism diopters of left exotropia is present preoperatively. Top right, Twenty-five prism diopters of left exotropia remains after scleral augmented transfer. Bottom left, Approximately 10 degrees of adduction is present in the left eye.

29 years. The patient recalled being told that the muscle responsible for pulling in the right eye was missing. Visual acuity was R.E.: 6/240 (20/800) and L.E.: 6/6 (20/20). Approximately 90 prism diopters of exotropia was present and the right eye was fixed in abduction (Fig. 3, left). A large coloboma involved the right optic nerve, and the left optic nerve was normal. A 2-cm vertical linear surgical scar was present on the upper lip from a previous midline cleft lip repair. Basal skull films taken during hospitalization showed a "deformation of the structures posterior to the soft palate" but no encephalocele.[5]

At surgery, passive ductions of the right eye showed marked resistance to adduction. The lateral rectus muscle was explored and was found approximately 15 mm posterior to the corneoscleral limbus.

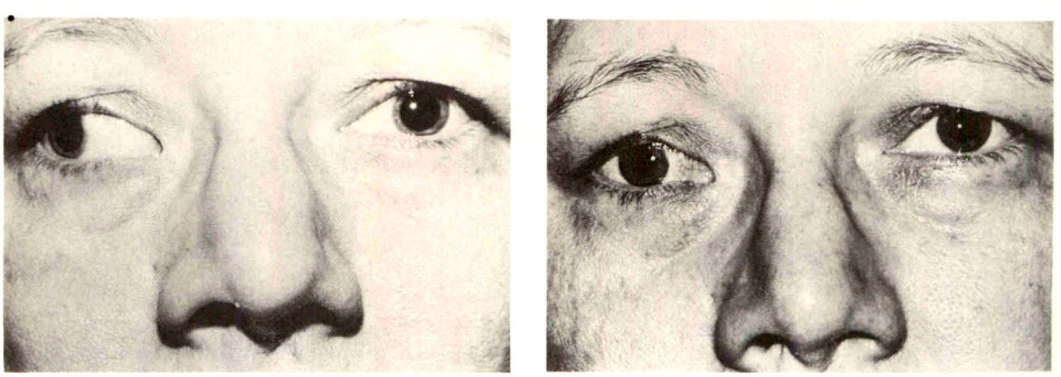

Fig. 3 (Helveston, Merriam, and Ellis). Case 2. Left, Ninety prism diopters of right esotropia is present preoperatively. Right, Twenty prism diopters of right esotropia remains after revision of the original scleral augmented transfer.

All restriction to passive adduction of the eye disappeared after disinsertion of the lateral rectus muscle. Careful dissection done on the medial aspect of the globe showed no evidence of the medial rectus muscle nor evidence that it had ever been present, confirming the patient's history.

A scleral augmented rectus muscle union was done as described previously. Three months later, because of a persistent right exotropia that measured 35 prism diopters, and a delle at the nasal corneoscleral limbus, the nasal side of the globe was re-explored. The original scleral band was identified where it had been sutured to the globe, and the bands of superior and inferior rectus muscle that had been pulled nasally were also identified. A 5-0 Merseline suture was placed around the slips of shifted tendon and were tightened, pulling the globe toward adduction. Additionally, the nasal conjunctiva was recessed. At her last visit, six months after the second surgery, the patient had 20 prism diopters of right exotropia and the delle had resolved (Fig. 3, right).

Discussion

Strabismus produced by a congenitally absent rectus muscle, traumatic section of a rectus muscle, or disinsertion after surgery is a challenge to the ophthalmic surgeon. Under these conditions, the eye is not only deviated but has little if any movement in the field of action of the missing muscle. Passive ductions, in nearly every case, become restricted in a matter of months because of contraction of the antagonist rectus muscle as well as loss of resilience of adjacent fascial structures.

When attempts are made to align such an eye, the initial surgical effort must be directed to relieving all existing restrictions, allowing free passive ductions. This routinely includes recession of the antagonist rectus muscle.

After the recession has been done and passive ductions are unrestricted, a tendon transfer procedure is needed. However, a full tendon transfer is ruled out because of the need for preserving anterior ciliary circulation. Jensen's rectus muscle union is impossible because there is no muscle to complete the union of the opposing rectus muscles. For this reason, the scleral augmented rectus muscle union as described previously seemed most expedient. On other occasions, we have attempted a type of procedure similar to Jensen's, where slips of opposing muscles are attached to sclera near the site of the missing muscle, but these efforts proved unsatisfactory. In special cases where a slipped muscle is treated promptly and restrictions of the antagonist requiring a recession are not present, a full tendon transfer may be done successfully and safely (M. M. Parks, personal communication, September 1978).

The function of the anterior ciliary circulation is not fully understood at this time. One surgeon suggested it is safe to remove all four rectus muscles.[6] We think this is unwise. Others advocate sparing two muscles or at least two anterior ciliary arteries.[7] Von Noorden,[8] while agreeing with this principle, pointed out that Jensen's rectus muscle union was designed to maintain two patent anterior ciliary arteries, and may indeed sacrifice more anterior circulation than anticipated if the distal anterior ciliary arteries follow an aberrant course. Study of the iris circulation after injection with fluorescein confirms that the blood flow in the iris can be affected by removal of extraocular muscles from the globe.[9] However, the role of the posterior ciliary artery remains unclear.

We believe that at least the lateral anterior ciliary artery or two other anterior ciliary arteries should be retained in individuals over 40 years of age. In such patients we do not consider it without risk to remove the only remaining anterior ciliary artery, even if surgery has been performed on the extraocular muscles months or years before.

Recently, two pertinent cases have been brought to our attention that emphasize this point. Each patient had a full tendon transfer of the superior and inferior rectus muscles, in one case ten years and in the second case more than 20

years after the horizontal recti had undergone a recession-resection procedure. Both patients developed anterior segment ischemic changes the day after surgery. In one case the reaction was mild and in the other severe. One patient (fortunately the one with a mild reaction) had the surgery done in his only remaining seeing eye. A similar case had been reported earlier by McNeer.[10]

Because of our concern for the integrity of the anterior segment of those eyes requiring extraocular muscle transfer for an absent muscle, the use of a scleral strip to facilitate the union of opposing rectus muscles over the site of the missing muscle proved to be a rational approach. From the experience in our two patients, it seems that special care should be taken to recess the conjunctiva over the site of the union to avoid the occurrence of a delle.

Summary

Two patients with 90 prism diopters of exotropia and an absent medial rectus muscle each had the nasal half of the superior and inferior rectus muscles joined with a thin strip of preserved sclera. The center of the scleral strip was first anchored to host sclera at the usual site of the medial rectus insertion. Alignment was improved in the primary position with a residual exodeviation of 25 prism diopters and 20 prism diopters, respectively. Each patient required secondary conjunctival recession because of a delle.

Acknowledgment

Gary S. Sandall, M.D., and Richard A. Saunders, M.D., provided information on patients with anterior segment ischemia.

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LATE RESULTS OF SUPERIOR OBLIQUE MUSCLE TENOTOMY IN TRUE BROWN'S SYNDROME

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Brown[1] described the superior oblique muscle tendon-sheath syndrome in 1950. Later, he identified two types, true and simulated sheath syndrome.[2]

In true Brown's syndrome elevation of the eye is limited in adduction so that the eye cannot voluntarily be raised above the midhorizontal plane. There is little or no overaction of the homolateral superior oblique muscle, usually slight downshoot of the eye, widening of the palpebral fissure on adduction, and an unequivocally positive traction test on attempted elevation in adduction. As the eye is abducted from its depressed position in full adduction, elevation follows a straight line to near full elevation to the normal limits on external rotation. There is almost normal muscle balance in the temporal field; on looking upward there is frequent limitation of elevation of the affected eye. This may also be the case with elevation in abduction. True Brown's syndrome may be typical or atypical.[2] Typically, there is no significant co-existing limitation of the homolateral superior rectus muscle; atypically there is a significant limitation.

In simulated Brown's syndrome, the posterior part of the superior oblique muscle and tendon is thickened, or too firmly attached to the posterior sheath, caused by inflammation extending from the ethmoid cells to the posterior sheath and tendon, from orbital floor fracture, or from frontal sinus surgery.

In 1976, one of us showed that complete superior oblique muscle tenotomy produced the best surgical results in 28 patients with true Brown's syndrome.[3] More recently, Webb Chamberlain, M.D. (personal communication, October 1978) found that gradual improvement may continue for several years postoperatively. Therefore, we studied the long-term results of superior oblique muscle tenotomy in patients who had true Brown's syndrome.

SUBJECTS AND METHODS

We searched the records of the 28 patients with true Brown's syndrome described in 1976.[3] Each patient had undergone a tendon-weakening procedure of the affected eye. We asked those who had undergone serial orthoptic assessments to return for re-assessment during 1978-1979. For each patient, we analyzed the immediate results of the superior oblique muscle tenotomy and the results at re-examination.

The orthoptic examinations consisted of assessment of ocular motility, head posture, determination of corrected visual acuity when possible (using the age-appropriate Snellen chart), assessment with cover and prism-cover tests at 6 and at ⅓ meters, including up, down, and lateral gaze, with and without refractive correction, assessment of the Lees screen, results of binocular single vision (that is Worth four-dot test at 6 and at ⅓ meters, synoptophore assessment, Tit-

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mus stereotest, and Bagolini glasses), and of diplopia, by the red-green dissociation method.

Results

Twelve patients had undergone serial orthoptic assessments; of these, nine were available for re-examination in 1978-1979, eight at the clinic and one by an ophthalmologist and orthoptist in another city. All patients had undergone complete superior oblique muscle tenotomy between 1967 and 1976 in which the tendon had been cut just medial to the superior rectus muscle. Age at surgery had ranged from 2 to 28 years; seven patients were aged 7 years or less. The re-assessment period ranged from three to 12 years. One patient had had atypical Brown's syndrome (Case 3); eight had had typical Brown's syndrome.

Case Reports

Case 1—A 5-year-old boy with right Brown's syndrome preoperatively had a compensatory chin-up head posture with a visual acuity of 6/6 (20/20) in both eyes (Fig. 1). In December 1974, a right superior oblique muscle tenotomy was performed; postoperatively the surgeon thought he might have missed the tendon. Orthoptic examination 20 days postoperatively showed minimal abnormal head posture with face turn to the left, improved motility, but some residual limitation of elevation and downshoot in adduction. There was no significant superior oblique muscle weakness. There was fusion at 6 and at ⅓ meters. In 1979 the child had no abnormal head posture and only minimal limitation of elevation; visual acuity was 6/5 (20/15) in both eyes, fusion remained unchanged, and stereoacuity was 40 seconds of arc. He had minimally symptomatic vertical diplopia on straight upgaze and levoelevation.

Case 2—In September 1972, right superior oblique muscle tenotomy was performed on a 2¾-year-old boy with right Brown's syndrome who had undergone preoperative occlusion of the left eye to improve vision in the amblyopic right eye. Postoperatively, he had minimal abnormal head posture (head tilt to the left and face turn to the right), minimal right superior oblique muscle weakness, and slight limitation of elevation in adduction of the right eye. Two years later his visual acuity was R.E.: 6/24 (20/80) and L.E.: 6/12 (20/40), and he had right esotropia of 6 prism diopters at 6 meters, 14 prism diopters at ⅓ meter, and right suppression at 6 meters, but fusion at ⅓ meter. Stereoacuity was limited to 3,000 seconds of arc. In 1979, the patient had no complaints and no evidence of abnormal head posture; his visual acuity was R.E.: 6/18 (20/60) and L.E.: 6/9 (20/30). Right superior oblique muscle weakness and limitation of elevation, fusion, and

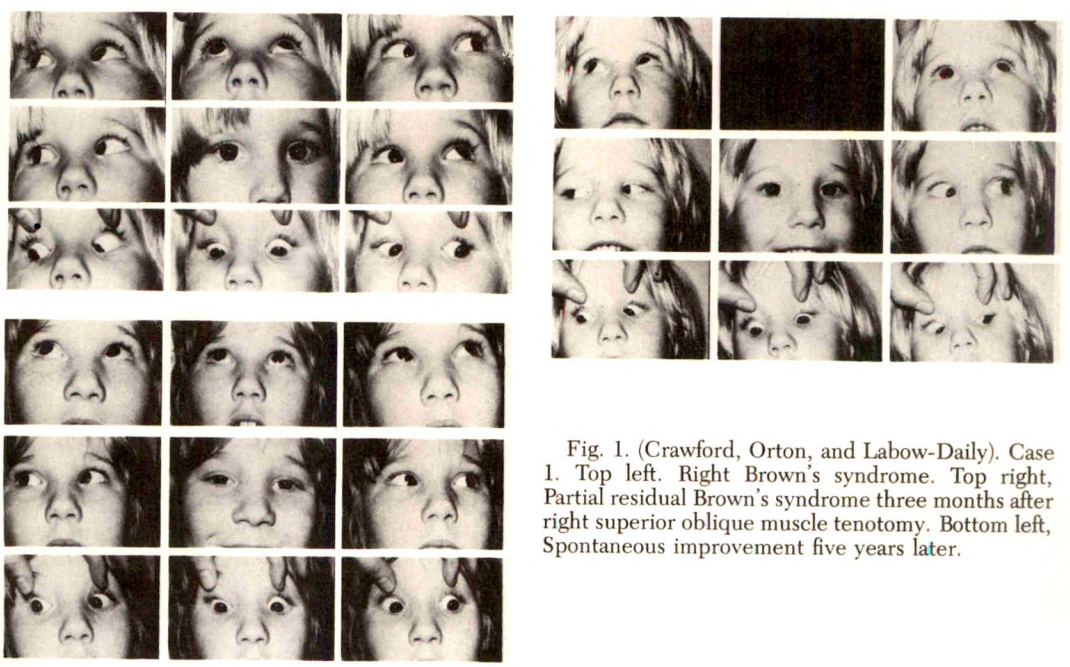

Fig. 1. (Crawford, Orton, and Labow-Daily). Case 1. Top left. Right Brown's syndrome. Top right, Partial residual Brown's syndrome three months after right superior oblique muscle tenotomy. Bottom left, Spontaneous improvement five years later.

stereoacuity remained unchanged; the esotropia was unchanged but was now associated with right hypertropia of 3 prism diopters.

Case 3—Preoperatively a 28-year-old woman had a left atypical Brown's syndrome with marked downshoot of the left eye on adduction, limitation of the homolateral superior rectus muscle, and secondary hypertropia of the right eye in upgaze. Left esotropia had been diagnosed at age 7 years. Her visual acuity was 6/6 (20/20) in both eyes with no abnormal head posture and no diplopia. There were positions of gaze where the eyes were straight and other positions where there was a manifest deviation; fusion was present at 6 and at ⅓ meters with stereoacuity of 40 seconds of arc. Superior oblique muscle tenotomy was performed in April 1976. Postoperatively, the vertical misalignment decreased; however, she had vertical diplopia. There was a left residual downdrift, limitation of elevation in adduction, and minimal limitation of the left inferior rectus and left superior oblique muscles; also, there was overaction of the right superior rectus muscle on elevation. During the next four months the diplopia resolved and ocular motility improved. Downshoot in adduction disappeared and limitation of the left eye and overaction of the right eye in upgaze decreased. The minimal limitation of the left eye on depression persisted and there was left hyperphoria of 2 prism diopters in the primary position. By 18 months postoperatively, the patient had an abnormal head posture with chin depression and had moderate limitation of the left eye on depression, and secondary overaction of the right eye on depression. Fusion and stereoacuity were retained. At that time a posterior fixation suture[4] without recession was performed on the contralateral inferior rectus muscle to relieve symptomatic diplopia in downgaze. Examination one year later showed symptomatic diplopia only in downgaze greater than 15 prism diopters below the horizontal plane, and restriction of the left eye in downgaze, but full movement in upgaze.

Case 4—Preoperatively, an 11-year-old girl with right Brown's syndrome had visual acuity of 6/5 (20/15) in both eyes, fusion at 6 and at ⅓ meters, and stereoacuity of 60 seconds of arc (Fig. 2). Immediately after superior oblique muscle tenotomy in November 1972, she had vertical diplopia in all positions of gaze. Also, a basic right exotropia of 8 prism diopters, a right hypertropia of 8 prism diopters in primary position, and moderate right superior oblique muscle paresis with moderate overaction of the right inferior oblique muscle had developed. Three months later she had intermittent diplopia only in upgaze. The superior oblique muscle paresis and inferior oblique muscle overaction improved spontaneously (exophoria, 2 prism diopters and right hyperphoria, 1 prism diopter in the primary position at 6 meters). In 1979, she was asymptomatic except for intermittent diplopia in upgaze when tired; she had full binocular single vision and full ocular motility with minimal right inferior oblique muscle overaction.

Case 5—A 5½-year-old boy with right Brown's syndrome and visual acuity of 6/6 (20/20) in both eyes underwent superior oblique muscle tenotomy in April 1970. Nine months later he had no diplopia and no abnormal head posture, improved ocular motility with moderate right superior oblique, and right inferior rectus muscle paresis, slight overaction of right inferior oblique and right superior rectus muscles, and minimal secondary overaction of the depressors of the left eye. At 6 and at ⅓ meters he had exophoria of 6 prism diopters with right hyperphoria of 3 prism diopters. Stereopsis was 60 seconds of arc. Two years later he continued to be asymptomatic but now had right hyperphoria of 14 prism diopters at ⅓ meter and 12 prism diopters at 6 meters, which broke down into right hypertropia with dissociation. He had mild head tilt to the left

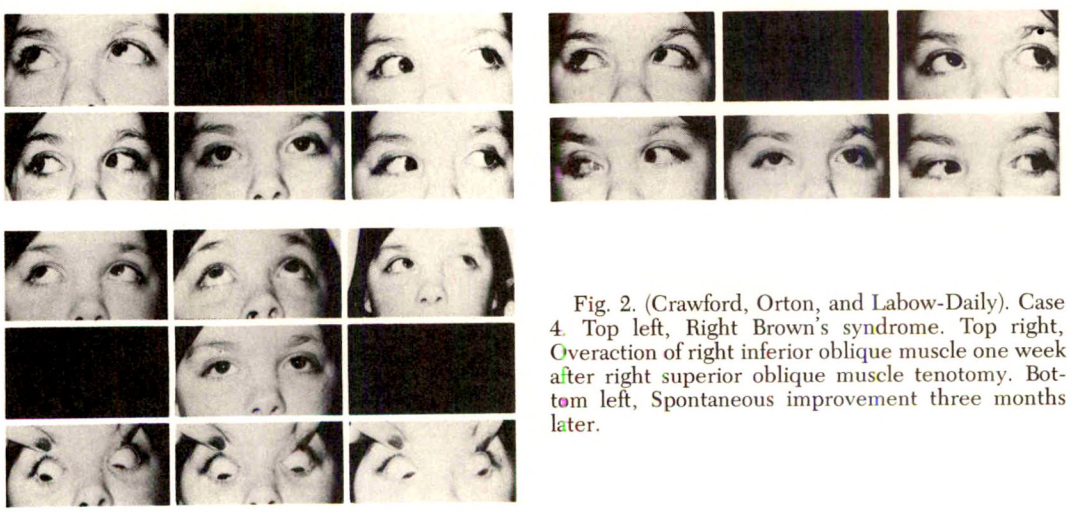

Fig. 2. (Crawford, Orton, and Labow-Daily). Case 4. Top left, Right Brown's syndrome. Top right, Overaction of right inferior oblique muscle one week after right superior oblique muscle tenotomy. Bottom left, Spontaneous improvement three months later.

and denied diplopia. Six years postoperatively his abnormal head posture had disappeared and he had exophoria of 2 prism diopters and right hyperphoria of 6 prism diopters at 6 and at ⅓ meters, but intermittent right hypertropia of 16 prism diopters in straight downgaze. Fusion and stereoacuity remained unchanged. Nine years postoperatively he was asymptomatic, had normal head posture, and visual acuity of 6/5 (20/15) in both eyes. His horizontal and vertical deviations and limitation of the right eye on depression remained unchanged. He continued to have fusion with stereopsis of 40 seconds of arc.

Case 6—A 6½-year-old boy with right Brown's syndrome underwent right superior oblique muscle tenotomy in December 1967. Six years postoperatively he had head tilt to the left and face turn to the right, associated with marked right superior oblique muscle paresis and marked secondary right inferior oblique muscle overaction. In primary position at ⅓ meter, he had exophoria of 6 prism diopters with a right hypertropia of 14 prism diopters, with and without his abnormal head posture, and at 6 meters he had right hyperphoria of 3 prism diopters with and right hypertropia of 8 prism diopters without the abnormal head posture. His visual acuity was 6/5 (20/15) in both eyes with stereopsis of 60 seconds of arc. Right inferior oblique muscle recession was recommended but his parents declined surgery. In 1979 the patient was asymptomatic, said he had no diplopia, and was unaware of cosmetically poor head posture. His visual acuity was 6/5 (20/15) in both eyes. With his abnormal head posture he had an exophoria of 2 prism diopters and a right hyperphoria of 5 prism diopters at ⅓ meter and right hyperphoria of 1 prism diopter at 6 meters. He showed marked right superior oblique muscle paresis and marked secondary right inferior oblique muscle overaction with an updrift of the right eye on adduction. The head-tilt test was positive for right superior oblique muscle paresis. There was fusion at 6 and at ⅓ meters with stereoacuity of 50 seconds of arc. The red-green dissociation test showed diplopia in levoelevation only. Again, the parents refused recommended surgery because he was asymptomatic.

Case 7—A 4-year-old girl with left Brown's syndrome, had V exotropic pattern with a basic alternating exotropia of 40 prism diopters. Visual acuity was R.E.: 6/9 (20/30) and L.E.: 6/12 (20/40) with left suppression at 6 and at ⅓ meters. Superior oblique muscle tenotomy was performed in February 1975. Four days postoperatively she had a basic alternating exotropia of 18 prism diopters and a left hypertropia of 6 prism diopters with a V exotropic pattern. Also, she had a mild left inferior oblique muscle overaction associated with mild left superior oblique muscle paresis. One year later, the alternating exotropia was 25 prism diopters with left hypertropia of 6 prism diopters, and she continued to have superior oblique muscle paresis and moderate inferior oblique muscle overaction. Left inferior oblique muscle myectomy, left lateral rectus muscle recession, and left medial rectus muscle resection were performed. In 1979 she was asymptomatic and had normal head posture and no diplopia. Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/12 (20/40), with residual, cosmetically acceptable basic alternating exotropia of 18 prism diopters and left hypertropia of 6 prism diopters in primary position. She still had slight left inferior oblique muscle overaction, secondary to the mild left superior oblique muscle paresis.

Case 8—A 4-year-old boy with right Brown's syndrome, associated with a slight V exotropic pattern, had visual acuity of 6/6 (20/20) in both eyes, fusion at 6 and at ⅓ meters, exophoria of 4 prism diopters, and intermittent left hypertropia of 3 prism diopters at 6 and at ⅓ meters. He also had a chin-up head posture. Right superior oblique muscle tenotomy performed in October 1972 showed that the superior oblique muscle tendon was two to three times the normal size. Two months postoperatively he had minimal head tilt to the left and face turn to the right with moderate right superior oblique muscle paresis and moderate secondary right inferior oblique muscle overaction. There was a basic right exotropia of 14 prism diopters and right hypertropia of 10 prism diopters, with right suppression at 6 and at ⅓ meters with and without abnormal head posture. Right inferior oblique muscle recession was performed in February 1973. The abnormal head posture and inferior oblique muscle overaction decreased and binocular single vision returned. One year later his status was unchanged; in 1979, his visual acuity was 6/5 (20/15) in both eyes and he had no complaints except minimal vertical diplopia, especially when attempting to play hockey. Also he had retained his abnormal head posture. He had exophoria of 2 prism diopters and intermittent right hypertropia of 2 prism diopters at 6 and at ⅓ meters with and without the abnormal head posture. The head tilt test was positive for right superior oblique muscle paresis and he had moderate updrift of the right eye on adduction with moderate residual right inferior oblique muscle overaction, and fusion was present at 6 and at ⅓ meters with stereoacuity of 40 seconds of arc. Vertical diplopia was evident in seven directions of gaze (except primary position and dextroelevation).

Case 9—A 2-year-old girl with right Brown's syndrome underwent superior oblique muscle tenotomy in February 1971. At the first postoperative assessment in December 1974 she had normal head posture, no diplopia, and full ocular motility with excellent binocular single vision. Her visual acuity was 6/7.5 (20/25) in both eyes. Four years later she had fusion at 6 and at ⅓ meters, stereoacuity of 40 seconds of arc, and visual acuity of 6/5 (20/15) in both eyes. Otherwise, her status was unchanged.

Discussion

The seven patients who had had excellent binocular single vision preoperatively maintained this during follow-up. The remaining patients (Cases 2 and 7) had significant horizontal deviation in primary position, preoperatively and postoperatively.

Shortly after complete superior

oblique muscle tenotomy, three patients had partial residual Brown's syndrome (improved ocular motility with residual limitation of elevation of the affected eye in adduction, associated with minimal or no paresis of the tenotomized superior oblique muscle) (Group 1); five patients had significant superior oblique muscle weakness (Group 2). The patient in Case 9 was not examined immediately postoperatively.

In patients in Group 1 (Cases 1-3), improvement of ocular motility was immediate, but there was residual limitation of elevation of the affected eye on adduction, with secondary overaction of the contralateral superior rectus muscle. In two patients (Cases 2 and 3), there was minimal weakness of the tenotomized superior oblique muscle also; in the other patient (Case 1) superior oblique muscle paresis had not been evident and motility improved during the five-year follow-up period. These results were not caused by inferior oblique muscle weakness: electromyographic recordings of the inferior oblique muscle in patients with Brown's syndrome are normal.[2,5,6] As the most common technical failure at surgery is missing the superior oblique muscle tendon,[3,7] the partial improvement in these patients may have resulted from inadvertent partial tenotomy. Alternatively, these patients may have undergone complete subtenon tenotomy that left the intermuscular septum intact, and therefore permitted the cut ends of the tendon to remain almost in apposition.[8]

The patient in Case 3, the only adult and the only patient with atypical Brown's syndrome, immediately postoperatively had partial residual Brown's syndrome with gradual improvement of ocular motility in upgaze over several months, but also showed increasing limitation of depression of the involved eye. This outcome is difficult to explain as a result of mechanical restriction secondary to the surgery.

All five patients in Group 2 (Cases 4-8) had superior oblique muscle paresis and secondary overaction of the homolateral inferior oblique muscle within a few weeks postoperatively; two improved spontaneously. In one case (Case 4) the paresis improved and the overaction decreased spontaneously within a few months. In Case 5, vertical deviation in primary position gradually increased and the paresis and overaction were moderate in the initial three years postoperatively; the condition gradually improved during the next three years and has been stable for the past three years. In Case 7 absence of binocular single vision may have presented an obstacle to the spontaneous improvement of the mild superior oblique muscle paresis and inferior oblique muscle overaction that occurred in patients with excellent binocular single vision. Marked paresis and overaction developed in Cases 6 and 8. Significant residual overaction remained at follow-up in 1978-1979 despite inferior oblique muscle recession in Case 8. Apparently, patients who have minimal or moderate superior oblique muscle paresis and minimal or moderate secondary overaction of the homolateral inferior oblique muscle and who have excellent binocular single vision improve spontaneously within several years. Group 3 comprised patients with marked superior oblique muscle paresis and inferior oblique muscle overaction who did not improve spontaneously; even after weakening of the homolateral inferior oblique muscle, some residual overaction may result.

Berke[9] showed that the amount of weakening of the superior oblique muscle could be varied by cutting or removing part of the tendon but leaving its sheath intact. Complete paralysis occurred if a portion of the tendon close to

the pulley and its sheath were excised. Parks[8] has shown that dissecting the anterior and posterior borders of the tendon from the intermuscular septum along its entire subtenon course, followed by tenotomy along the medial border of the superior rectus muscle, produces a high incidence of superior oblique muscle palsy. Possibly, in our patients, the superior oblique muscle paresis resulted from complete tenotomy, with cutting of the entire sheath or dissection of the adjacent intermuscular septum.

We conclude that if marked superior oblique muscle weakness and homolateral inferior oblique muscle overaction develop, surgery should be performed on the latter muscle; if superior oblique weakness is mild or moderate and binocular single vision is excellent, the condition improves spontaneously.

The patient in Case 9, whose first reexamination was three years after surgery, showed a normal head posture, no diplopia, and full ocular motility with excellent binocular single vision. We do not know whether she would have been in Group 1 or Group 2 if she had been examined immediately postoperatively.

Summary

We re-assessed nine patients (aged 2 to 28 years) in whom true Brown's syndrome had been diagnosed and superior oblique muscle tenotomy performed. The postoperative period ranged from three to 12 years. The final results were divided into three groups: (1) Patients with partial residual Brown's syndrome postoperatively who gradually improved spontaneously over several years, with one exception. (2) Patients who had minimal or moderate superior oblique muscle paresis, secondary overaction of the homolateral inferior oblique muscle, and excellent binocular single vision postoperatively who improved spontaneously. In Groups 1 and 2, the study showed that the long-term results are better than those immediately after surgery, and the surgeon should not be too hasty in reoperating. (3) Patients with marked superior oblique muscle paresis and secondary homolateral inferior oblique muscle overaction postoperatively did not improve spontaneously and required a weakening procedure on the homolateral inferior oblique muscle.

Acknowledgment

J. A. Pratt-Johnson, M.D., provided follow-up data for Case 3.

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AN INTEGRATED APPROACH TO VITRECTOMY INSTRUMENTATION

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Since the introduction of pars plana vitrectomy surgery by Machemer and associates,[1] many vitreous suction cutters have been developed, powered both electrically[1-6] and pneumatically.[7,8] Additionally, the following ancillary techniques in vitrectomy have been developed and have required additional instrumentation: lens fragmentation,[9,10] simultaneous fluid-gas exchange,[11] evacuation of preretinal blood,[12] internal drainage of subretinal fluid,[13] fluid infusion via a handheld needle, pars plana or corneal cannula,[8] backflush maneuvers for clearing instrumentation, unipolar[14] or bipolar endodiathermy,[15] and fiberoptic endoillumination.[16] Klöti[4] introduced a manifold instrument tray for use with his vitreous stripper.

I devised an instrument tray that allows a uniform approach to providing infusion, suction, electrical or pneumatic power for a variety of vitrectomy systems and auxiliary equipment used in both anterior and posterior vitrectomy surgery. Additionally, I describe a uniform approach to the organization of the operating room and operating table for vitrectomy surgery.

MATERIAL AND METHODS

The main features of the integrating manifold instrument tray* that I have designed are shown in Figures 1 and 2. The instrument tray is placed on a Mayo stand over the patient's chest. A set of four pinch valves on either side of the tray can be selected for supplying suction instruments and the remaining four pinch valves for supplying the infusion instruments. Each instrument is connected to the appropriate pinch valve with medical grade silicone tubing of uniform diameter and length. Instruments that are already supplied with differing diameters and types of suction tubing are connected to the silicone tubing used on this tray with a tapered Luer connector and a female Luer fitting, which is supplied with the silicone tubing set (Fig. 3). Those instruments supplied with female endings are connected with double-ended male connectors (Fig. 4) and those instruments supplied with male endings are connected directly

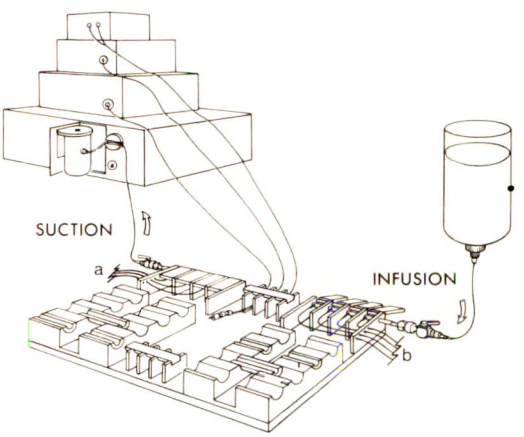

Fig. 1 (Stern). A diagrammatic representation of the vitrectomy instrument integrating tray displaying the pinch valves connected to the infusion fluid and the automatic suction console. Individual instruments are connected to the pinch valves with medical grade silicone tubing (a,b). Electrical power lines, fiberoptic lines, and diathermy lines are guided through central gates on the tray.

*Manufactured by Precision Medical Instruments, 250 Bay View Ave., Belvedere, CA 94920.

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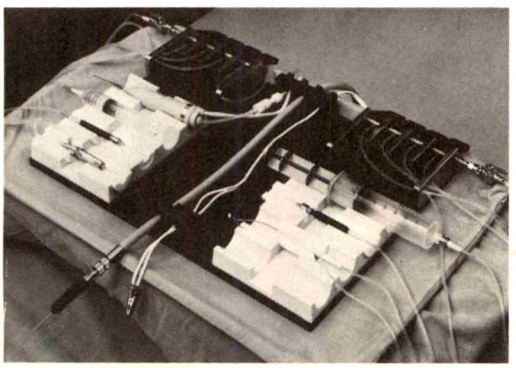

Fig. 2 (Stern). The integrating tray with a variety of vitrectomy instruments placed in the silicone moldings is seated on a Mayo stand over the patient's chest.

to the female ending on the standardized silicone tubing.

Suction is supplied to the set of four valves either by a syringe in those systems using manual suction or by a slight modification of the suction tubing in those systems using automatic suction. Although modified twin bore suction tubing that is used for the Ocutome system is shown, similar modifications of the suction tubing can be used for other automatic suction vitrectomy systems.

The electrical lines used to supply power to a variety of suction cutters and lens fragmentors are guided through central gates on the instrument tray and connected to the various power consoles (Fig. 2). Infusion instruments are similarly connected to the set of four pinch valves using uniform diameter medical

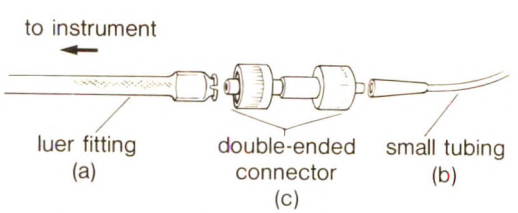

Fig. 4 (Stern). A diagrammatic representation of the method by which instruments with female Luer fittings (a) are connected to the silicone tubing via a double-ended male connector (c).

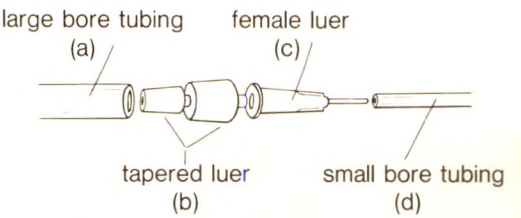

Fig. 3 (Stern). A diagrammatic representation of the method by which large bore tubing (a) is connected via a tapered Luer fitting (b) to the small bore silicone tubing (d) supplied with a female Luer fitting (c).

grade silicone tubing supplied with the appropriate Luer fittings. A single infusion fluid bottle is needed to supply all of the infusion instruments. If a full function probe is desired in which suction and infusion are simultaneously supplied to the probe, the suction line to the probe is connected to the suction valve and the infusion line is connected to the infusion valve.

Suction and infusion to all instruments are controlled uniformly with pinch valves to compress the silicone tubing. If automatic suction is used, all of the suction instruments are connected to a single suction line, thus placing all suction instruments under foot switch control.

Diathermy and fiberoptic light cords are guided through central gates onto the operating field (Fig. 2). Instruments of various sizes are held in place in silicone moldings. Inserts are provided to accommodate smaller diameter instruments (Fig. 5). The silicone moldings provide friction, which holds the instruments firmly in place.

Backflushing of the suction instrument is done by closing the one-way stopcock to the suction syringe or automatic suction console and opening the appropriate manifold pinch valve connecting the backflush syringe and instrument to be cleared.

Fluid-gas exchange is performed in a

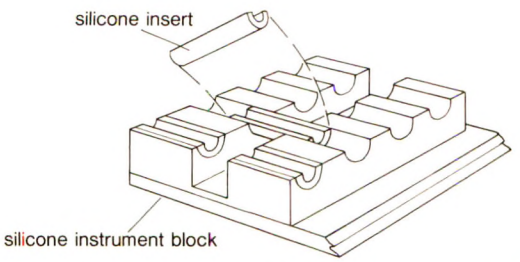

Fig. 5 (Stern). A diagrammatic representation of the silicone molding with silicone inserts used for holding instruments of various sizes.

similar manner by closing the one-way stopcock connected to the fluid infusion bottle and opening the pinch valves connecting the air- or gas-filled syringe with the infusing cannula or needle.

Discussion

Many of the problems of arranging the equipment and the operating room can be managed when using the integrating manifold instrument tray. The nonsterile side of the operating table is designated as a side on which the various instrument consoles are placed (Fig. 1). The set of valves closest to the consoles is designated as the side on which the suction cutter and lens fragmenting instruments are placed to facilitate the placement of the various suction and electrical power cords (Fig. 1). The instrument tray is completely modular so that all instruments can be connected either to the right- or left-hand side of the tray, thus permitting the surgeon to choose the side of the operating room table on which he wishes to place his instrument consoles. Additionally, the instrument consoles can be placed over the operating table behind the manifold instrument tray.[17]

Before beginning surgery, each instrument to be used can be systematically connected to the appropriate infusion or suction manifold valve and the instrument can be tested. The systematic manner in which the vitrectomy instruments are organized enhances the versatility of the surgeon using different instruments sequentially.

Other vitrectomy systems that may be used in an operating room by different surgeons can be set up in a similar fashion. The standardized pinch valves are easy to operate and select, thus decreasing the need for a skilled assistant and enhancing the surgeon's control over the operative procedure.

Summary

I devised a vitrectomy instrument integrating tray for a variety of vitrectomy systems. The tray controls the infusion and suction instrumentation through pinch valves, provides pathways for fiberoptic, diathermy and electrical cords, and provides silicone moldings for holding the various instruments used in vitrectomy surgery.

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Fifty years ago this month in *The Journal*

The long known causes of chronic iritis, syphilis, rheumatism, gout, and tuberculosis, generally begin with an acute attack. The same is true of the focal infections, now recognized as causes of many disturbances formerly classed as "rheumatic." These must not be ignored in connection with any acute attack; and there are other causes that are less common, but just as important to remember. An iritis which is at first acute may be brought on by chronic constipation with absorption of intestinal toxins, by diabetes, or by arthritis deformans. Infective jaundice due to a spirochete is often marked by uveitis. Ophthalmic herpes zoster may cause it. The acute contagious fevers may be followed by it. The search for the real cause of an acute iritis often needs to be long and difficult. But it is worth making, both to cure the attack and to prevent its sequels and recurrence. The first scientific meeting of the Association for Research in Ophthalmology, to be held at Detroit, June 24th, is to be devoted to the etiology of acute iritis. The more we learn of the etiology the more thorough can be our search for the diagnosis of iritis.

Edward Jackson, *The Diagnosis of Acute Iritis*

Am. J. Ophthalmol. 13:538, 1930

CILIORETINAL CIRCULATION AND BRANCH ARTERIAL OCCLUSION ASSOCIATED WITH PRERETINAL ARTERIAL LOOPS

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Since the initial description of the preretinal arterial loop by Liebreich in 1871,[1] only four cases associated with branch retinal arterial occlusion have been reported.[2-5] Three of these occlusions have occurred in patients aged 19 to 22 years. Brown and associates[5] described the fluorescein angiographic appearance of a case of unilateral branch artery occlusion in a patient with bilateral preretinal arterial loops. This was the first report in which the primary arterial blood supply in each eye was cilioretinal in origin.

We report three additional cases of occlusion of a preretinal arterial loop with branch retinal arterial occlusion in which a similar cilioretinal circulation is shown. This confirms the observation made previously that eyes with such loops also may have abnormal vessels supplying both retina and choroid. Whether presence of such cilioretinal arterial supply predisposes to the occlusion of the preretinal arterial loop is uncertain.

CASE REPORTS

Case 1—A 26-year-old woman was seen in September 1977. Twenty-four hours before this visit she had a sudden and complete loss of the upper half of the left visual field without premonitory symptoms. She had been taking birth control medication for four years before this episode. Medical and family history were noncontributory. After hospital admission, results of examination and laboratory tests were normal, including hemoglobin electrophoresis. Visual acuity was R.E.: 6/6+2 (20/20+2) and L.E.: 6/4.5 (20/15). The right fundus was normal; the left fundus showed a vascular loop passing forward from the optic disk partially covered by glial tissue. The ascending and descending portions of the loop appeared to be formed by the inferior branch of the central retinal artery before it supplied the inferior temporal retina. The descending portion was markedly narrowed, and diffuse retinal edema was present (Fig. 1). Segmentation of the blood column was present along the inferior temporal arteriole with gentle globe pressure. Goldmann perimeter field

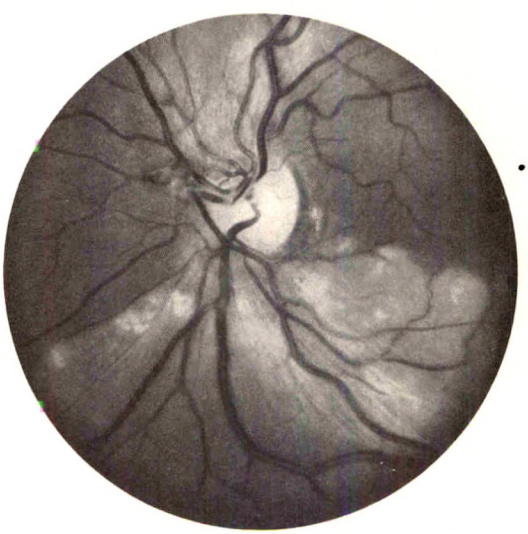

Fig. 1 (Limaye, Tang, and Pilkerton). Case 1. Preretinal arterial loop with associated nerve fiber layer edema.

From the Center for Sight, Department of Ophthalmology, Georgetown University Medical Center, Washington, D.C. This study was supported in part by an unrestricted research grant from Research to Prevent Blindness, Inc. This paper was presented in part at the Retina Society, Twelfth Scientific Meeting, Sept. 8, 1979, Sea Island, Georgia (Dr. Pilkerton).

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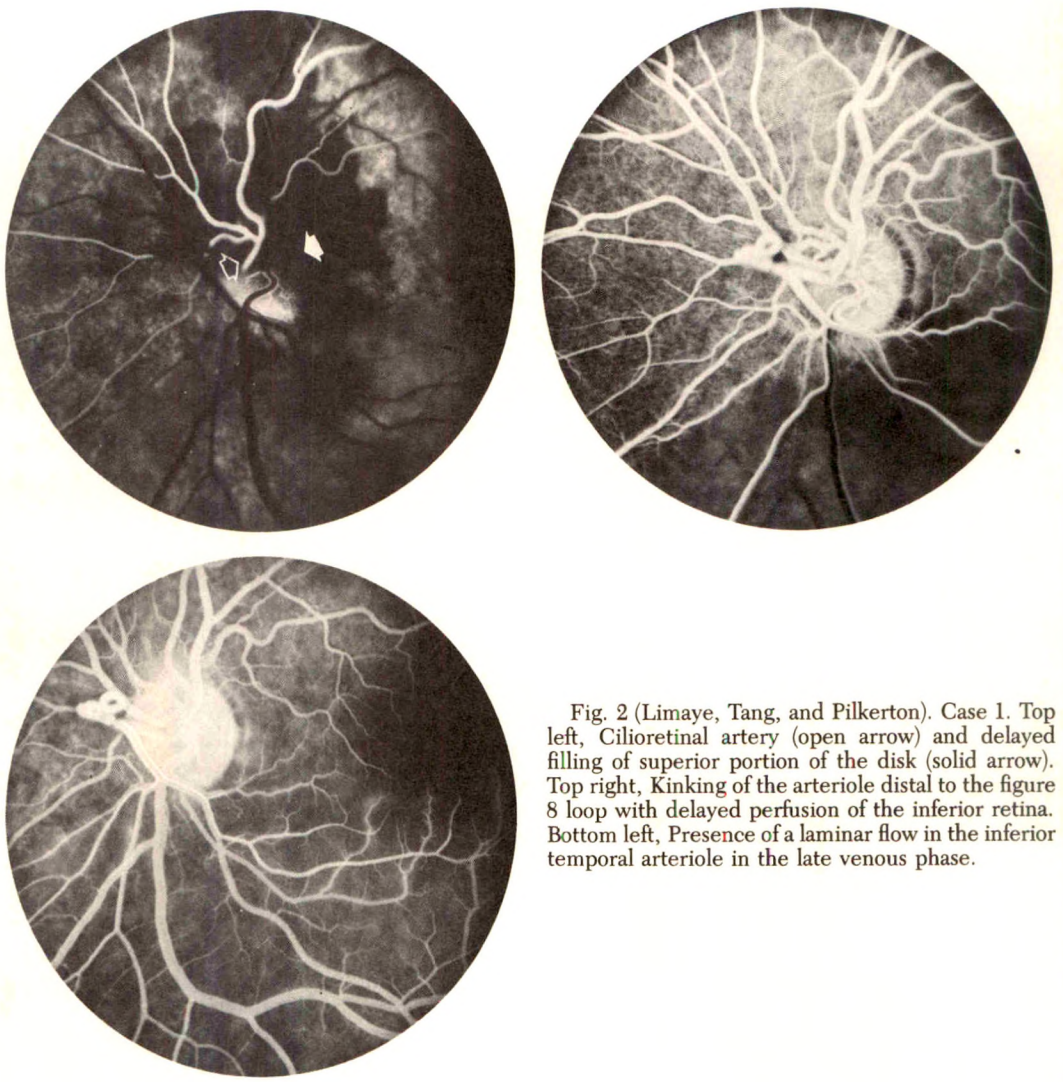

Fig. 2 (Limaye, Tang, and Pilkerton). Case 1. Top left, Cilioretinal artery (open arrow) and delayed filling of superior portion of the disk (solid arrow). Top right, Kinking of the arteriole distal to the figure 8 loop with delayed perfusion of the inferior retina. Bottom left, Presence of a laminar flow in the inferior temporal arteriole in the late venous phase.

testing showed an absolute superior altitudinal defect. Ophthalmodynamometry did not show significant side to side difference in ophthalmic artery pressures.

In the fluorescein angiogram at 9.4 seconds, the superior trunk appeared to be a cilioretinal artery irrigating most of the choroid and the retina except that area supplied by the inferior temporal arteriole. At this stage the lower half of the disk was well perfused. The upper half remained nonperfused (Fig. 2, top left).

A delay of 2.0 seconds was required for the dye to pass from the preloop portion of the inferior temporal arteriole to the postloop portion of the arteriole. At 13.9 seconds, inferior to the figure 8 loop, a kinking of the ateriole was visible along with a marked delay in filling of the branches of inferior retinal arteriole (Fig. 2, top right). Laminar flow in the inferior temporal arteriole was seen in the late venous phase at 46.4 seconds (Fig. 2, bottom left). The superior temporal retinal arteriole appeared essentially as a ciliary vessel; the lower temporal vessel arteriole forming the loop was a retinal arteriole. The anastomosis of these two vessels forms a cilioretinal anomaly.

Fluorescein angiography was repeated three weeks later. At this time the spiral loop was completely obstructed, the loop was reduced in caliber, and appeared stretched along its axis with some surrounding glial tissue. Some extravasation of the

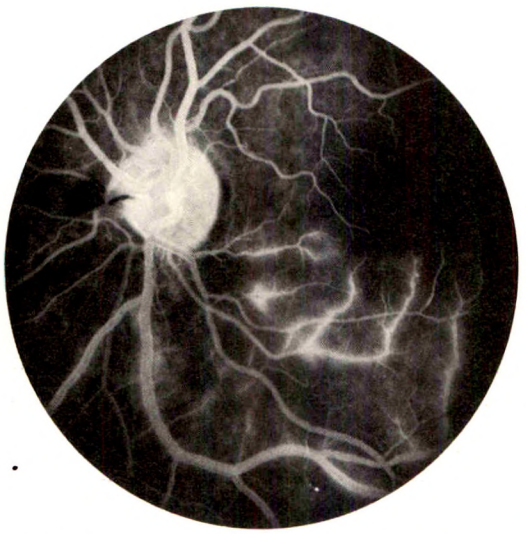

Fig. 3 (Limaye, Tang, and Pilkerton). Case 1. Three weeks later the loop is completely obstructed with vessel wall leakage.

dye from the vessels inferior to the macula was observed (Fig. 3). Fluorescein angiography of the right eye was unremarkable.

Case 2—A 14-year-old girl was seen in January 1979 because of sudden loss of the lower half of the right visual field of several hours' duration. Medical and family history were unremarkable. Results of physical examination and laboratory tests' including hemoglobin electrophoresis were normal.

Visual acuity was R.E.: 6/7.5 (20/25) and L.E.: 6/6-2(20/20-2). The only abnormality noted was a spiral preretinal arterial loop passing forward from the disk and moving freely in the vitreous of the right eye. An area of retinal edema and nerve fiber layer infarcts was noted along the course of the superior retinal arteriole (Fig.4, left). A photograph obtained six months before this occlusive episode showed an asymptomatic preretinal loop for comparison (Fig. 4, right). Goldmann perimeter field testing showed an absolute inferior temporal defect.

Fluorescein angiography at 8.3 seconds showed two prominent temporal and inferior cilioretinal arterioles (Fig. 5, top left). At 12.8 seconds, the dye was seen in the afferent portion of the loop. The efferent portion of the loop and its continuation of the superior temporal arteriole remained unfilled. Distal to the obstruction, two branches of the superior temporal arteriole were being fed by prominent compensatory radial peripapillary capillaries (Fig. 5, top right). There seemed to be communication between the superior temporal veins and the superior temporal arteriole distal to the obstruction. At 431.5 seconds, a granular filling defect was seen in the efferent portion of the loop (Fig. 5, bottom left). On repeat fluorescein angiography three months later, the loop still appeared to be incompletely blocked.

Case 3—In February 1979 a 60-year-old man had acute loss of his left inferior visual field of five days' duration. He had essential hypertension of three years' duration, well-controlled with 250 mg of alpha methyl levadopa twice daily. Medical and family

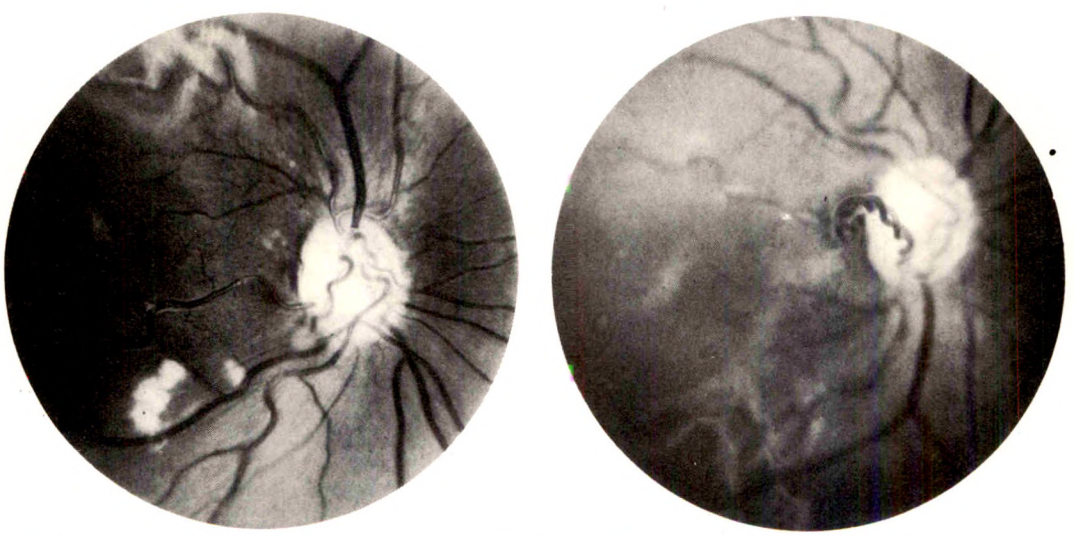

Fig. 4 (Limaye, Tang, and Pilkerton). Case 2. Left, Preretinal loop with associated nerve fiber layer edema. Right, Preretinal loop before the occlusion.

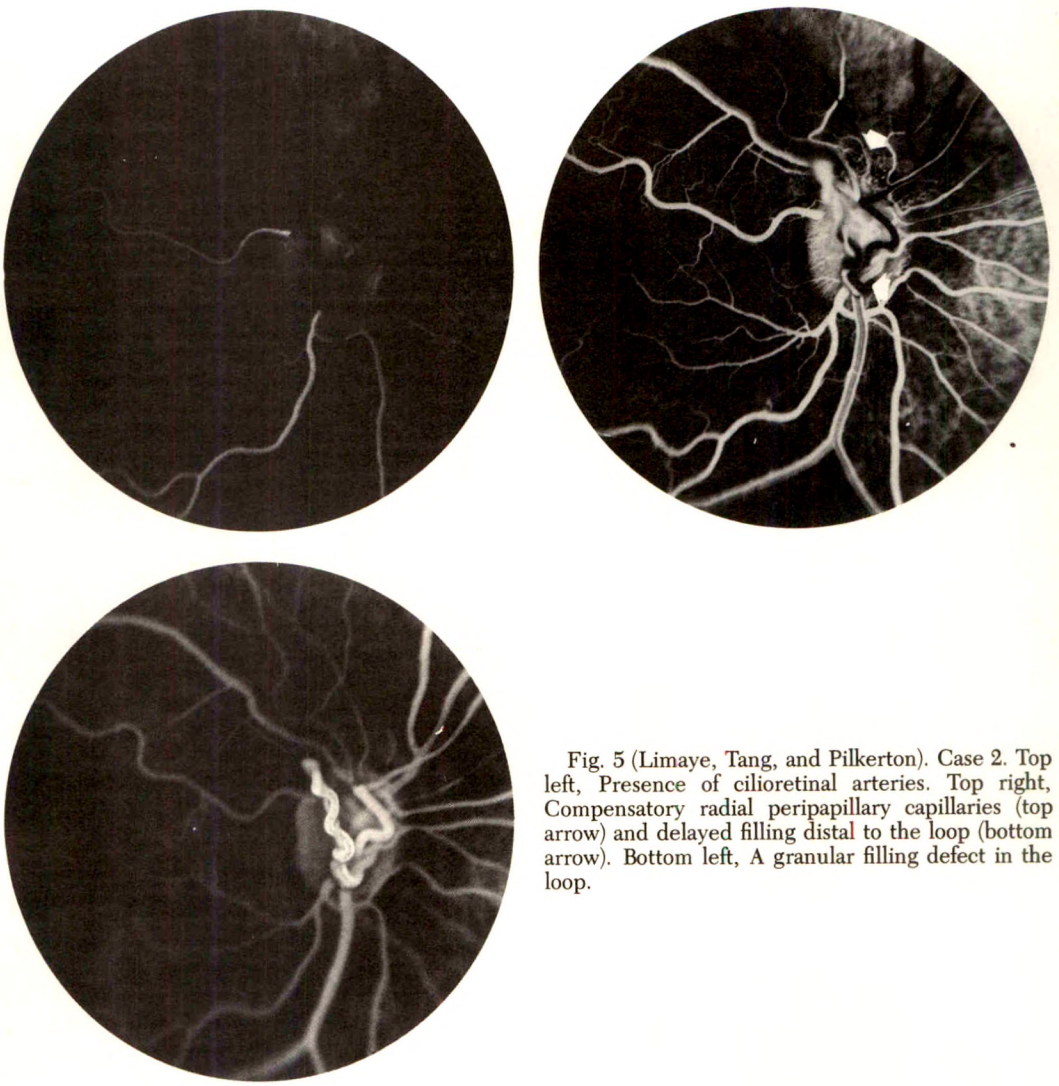

Fig. 5 (Limaye, Tang, and Pilkerton). Case 2. Top left, Presence of cilioretinal arteries. Top right, Compensatory radial peripapillary capillaries (top arrow) and delayed filling distal to the loop (bottom arrow). Bottom left, A granular filling defect in the loop.

history were noncontributory. Results of laboratory tests including hemoglobin electrophoresis were normal.

Visual acuity was R.E.: 6/6-1(20/20-1) and L.E.: 6/7.5-1(20/25-1). Results of the rest of the examination were normal, except for retinal edema along the course of the left superior temporal arteriole extending down to, but not including, the macular area. The arteriolar loop was connected to the upper temporal arteriole and extended into the vitreous. Goldmann perimeter testing showed absolute inferonasal defect. Ophthalmodynamometry showed no significant side differences in the ophthalmic artery pressures.

Fluorescein angiography showed an inferior and nasal cilioretinal circulation with delayed and incomplete filling of the loop and superior temporal arteriole (Fig. 6). Repeat angiography one month later showed an attenuated and poorly filled loop (Fig. 7). Angiography of the right eye was normal.

Discussion

The preretinal arterial loop is a congenital anomaly that originates from a main branch of the central retinal artery on the optic disk. Embryologically these loops are derived at about the 100-mm stage from within the area of Bergmeister's papilla and have no connection with the hyaloid artery.[7] The loops may

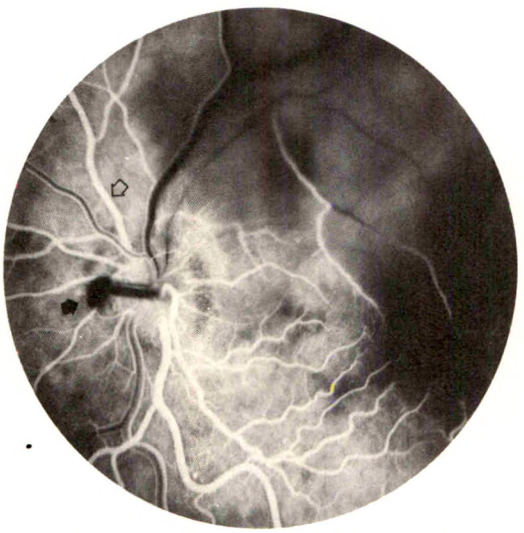

Fig. 6 (Limaye, Tang, and Pilkerton). Case 3. Poorly filled preretinal loop (solid arrow) with poor perfusion of the superior retina, cilioretinal artery (open arrow).

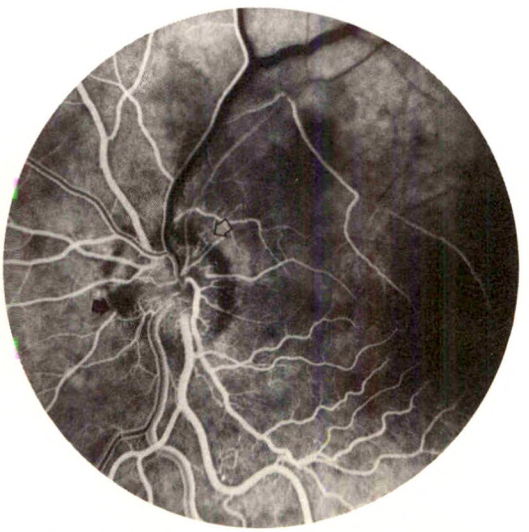

Fig. 7 (Limaye, Tang, and Pilkerton). Case 3. Attenuation of the loop (solid arrow) and compensatory radial peripapillary capillaries (open arrow).

be single or take more spiral turns. They may enter and exit at the disk and continue into the retina as a branch arteriole.[8] Additionally there seem to be two types of preretinal loops, one connected to retinal circulation (Fig. 8) and another connected to cilioretinal circulation. Our three patients belong to the latter group. The cause of occlusion is thought to be kinking or twisting of the loops, but the precise mechanism is unclear.[4]

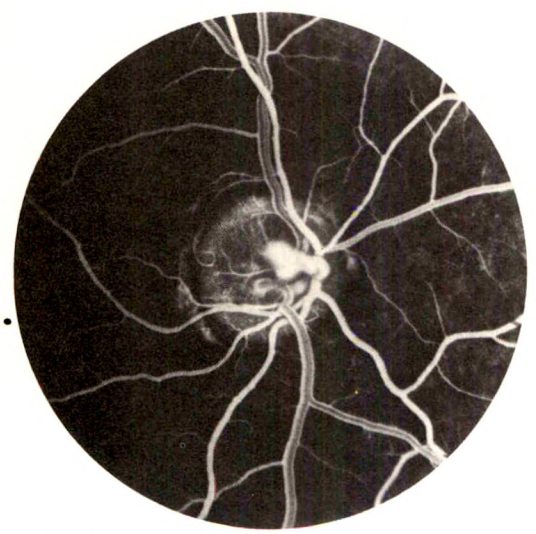

Fig. 8 (Limaye, Tang, and Pilkerton). A preretinal loop without significant cilioretinal arteries.

The extensive cilioretinal circulation seen in these three cases is similar to that noted in the case of Brown and associates.[5] The association of such extensive cilioretinal circulation in five eyes of four patients thus far described with fluorescein angiography suggests that preretinal loops may be a part of cilioretinal vascular anomaly.

Summary

Three patients had occlusion of preretinal loops and associated branch arterial occlusion. On fluorescein angiography all three eyes showed extensive cilioretinal circulation and that the occluded preretinal loops were part of the cilioretinal vascular anomaly. This supports the hypothesis that one form of preretinal

arterial loop is associated with a malformation of the cilioretinal circulation.

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THROMBOTIC THROMBOCYTOPENIC PURPURA WITH OPTIC DISK NEOVASCULARIZATION, VITREOUS HEMORRHAGE, RETINAL DETACHMENT, AND OPTIC ATROPHY

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Thrombotic thrombocytopenic purpura is a rare disorder first described by Moschcowitz[1] in 1925. Since then several hundred cases have been described in published reports. Among the many complications associated with this disease, ocular manifestations are relatively common. However, to the best of our knowledge, this is the first published report of a patient with neovascularization of the disk and optic atrophy complicating thrombotic thrombocytopenic purpura.

CASE REPORT

A 33-year-old woman was admitted elsewhere on April 30, 1978, because of abdominal pain and rectal bleeding. Before admission, she had been bleeding rectally for five days and had been nauseated and vomiting for four days. She reported she had been consuming large quantities of alcohol daily for more than two years. During that period her nutritional status had become impaired. On admission she had not eaten well for more than two weeks. Her only reported medication was an oral contraceptive.

On admission her vital signs were as follows: temperature, 37.5°C; pulse, 128/min, and blood pressure, 114/80 mm Hg. White blood cell count was 11,300/mm^3, with 84% neutrophils, 11% lymphocytes, 3% bands, 2% monocytes, and hemoglobin of 14.5 g/100 ml. Red blood cell indices were within normal limits and the platelet count was normal. Urinalysis showed pink urine with 3+ (300 mg/dl), protein, specific gravity of 1.025 and pH 5.5 with many coarse and fine granular casts. No white blood cells nor crystals were seen. Urobilinogen was increased at 4.0 mg/24 hr. Three days later, blood urea nitrogen was 59 mg/100 ml; total bilirubin was 2.5 mg/100 ml with 0.9 mg direct (conjugated). Lactic dehydrogenase was 2,800 IU/L with serum glutamic oxaloacetic transaminase also increased at 450 IU/L. Alkaline phosphatase level was 115 IU/L. An X-ray of her abdomen was read as negative at that time.

The patient continued to pass bright red blood rectally, was given nothing by mouth, and was administered intravenous fluids. Her gait deteriorated. She was mentally confused and her speech was slurred. Her condition developed into what was diagnosed as a convulsive disorder, grand mal type, attributable to withdrawal of alcohol. These symptoms were treated successfully with phenytoin sodium, phenobarbital, and diazepam. On May 2, 1978, she was given hyperalimentation to supplement her low food retention that resulted from constant emesis.

Physical findings at that time were unremarkable. No hepatosplenomegaly was noted. A peripheral blood smear showed a large number of polychromatophils with an occasional nucleated red blood cell. Many fragmented erythrocytes were seen with a number of spherocytes present. Platelets were markedly reduced to about 25,000/mm^3, most of them large. Her bone marrow was hyperplastic with adequate to increased megakaryocytes. Vacuoles were present in the cytoplasm and nuclei of cells in both red and myeloid series. Prothrombin time and partial thromboplastin times were within normal limits. Fibrinogen split products were measured at 80 g/100 ml with fibrinogen reaching a peak of 600 mg/100 ml one week later. The clinical diagnosis was thrombotic thrombocytopenic purpura.

She was transferred to the intensive care unit where she was tremulous with mumbling speech, grossly confused, and disoriented. All bowel movements were bloody with a fair amount of mucus. She had renal failure and became anuric. On May 4, 1978, she had blood urea nitrogen of 88 mg/100 ml with a creatinine of 8.2 mg/100 ml and normal electrolytes. Multiple hemodialyses during the next two months slightly improved her central nervous system irritability. Renal biopsy results were consistent with a diagnosis of renal cortical necrosis secondary to thrombotic thrombocytopenic purpura. Sections of the renal biopsy showed no staining with fluorescent anti-immunoglobuin antibodies nor with anti-C_3 antibodies.

Splenectomy was performed on May 4, 1978, without complications. Pathologic examination

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showed passive congestion with hyperemia. After splenectomy the patient regained her orientation. Platelet count began to rise from a nadir of 5,000/mm^3 after splenectomy. She was given prednisone for her thrombotic thrombocytopenic purpura and subsequently developed a respiratory infection requiring volume respirator intubation. This infection was successfully treated.

The patient then seemed stable on a regimen of prednisone, aspirin, and dipyridamole. However, the hematocrit continued to decrease despite multiple transfusions and reached a low of 19% with a hemoglobin of 5.2 g/100 ml on July 31, 1978. Also, arterial blood gas values showed a PO_2 of between 35 and 60 mm Hg while breathing up to 45% oxygen between May 24, and July 15, 1978, during which time she was semicomatose.

Decreased vision was first noted by the patient upon awakening from her semicomatose state. Subsequent decreased vision was reported to have taken place during the remainder of her hospitalization.

She was transferred to another hospital for chronic dialysis on Aug. 5, 1978. Within two weeks urine output began to increase, allowing discontinuation of hemodialysis after 103 days. By then, bilateral atrophic changes were easily observed in the optic disks. Hazy peripheral vision was all that remained two months later.

During the middle of November 1978, the patient had an intense itching of her right eye, which she rubbed vigorously. Subsequently, a vitreous hemorrage occurred in that eye. A computed axial tomography scan performed in early December 1978 to detect a relapse of her disease showed no abnormalities.

On Jan. 4, 1979, extensive hemorrhage caused a sudden decrease in vision in her left eye. At that time hemoglobin was 12.4 g/100 ml, hematocrit was 38.3 g/100 ml, white blood cell count was 7,400/mm^3, and platelet count was normal.

On Jan. 6, 1979 the patient was referred to us with a diagnosis of vitreous hemorrhage and optic atrophy. At the time of her first visit, visual acuity was R.E.: 1/80 (5/400) and L.E.: counting fingers at one foot. Applanation pressure was R.E.: 18 mm Hg and L.E.: 16 mm Hg. Pupils were normal with no definite pupillary defects identified. Blood pressure was 120/80 mm Hg. No carotid bruits were heard. Ophthalmoscopic examination of the right eye showed fibrovascular proliferation along the superior temporal arcade. Definite optic atrophy was present on the right side with pallor of the disk. There was extensive vitreous hemorrhage that was settled mainly in the inferior vitreous. Through the hemorrhage some attenuation of the retinal arterioles was visible. However, no severe narrowing or copper wire changes were observed. No abnormal arteriovenous crossing changes were seen. No collateral vessels were seen in the visible portions of the fundus.

The left eye showed neovascularization of and around the disk in several locations. The appearance of the disk was that of optic atrophy, but this was more poorly defined than in the right eye. Vitreous hemorrhage in the left eye was considerable and hindered examination of the vessels. A fluorescein angiogram was performed (Fig. 1).

The patient was admitted here on Jan. 29, 1979. She underwent peripheral retinal scatter treatment to the right eye with 500-μ spot-sized argon laser lesions wherever the view of the fundus was sufficiently clear (outside the macula). Treatments were added as clearing of the hemorrhage allowed on a regimen of elevation, closed eyes, and limited activity. Each photocoagulation session consisted of more than 500 applications of 500 μ in diameter, each with a duration of 0.1 to 0.2 seconds. Intensity varied up to 1,200 mW. More than 2,000 lesions were placed. The patient tolerated each of these procedures well.

By March 1979, significant clearing of the vitreous hemorrhage in the right eye was noted, with some improvement in vision. No new hemorrhage had occurred. However, when she was seen July 21, 1979, a detachment of the retina in the fellow eye was seen through the clearing vitreous hemorrhage and was confirmed by ultrasound (Fig. 2). She was re-admitted here July 23, 1979, for surgical repair.

On July 24, 1979, the patient underwent pars plana vitrectomy with meridional silicone sponge exoplant and a 360-degree encircling band. A three-incision technique with sutured infusion cannula was used. All vitreous blood was removed with the exception of a small peripheral rim of blood. The fibrovascular proliferations from the disk noted at surgery to insert on the detached inferior retina were cut. Indirect ophthalmoscopy with 360 degrees of scleral depres-

Fig. 1 (Lewellen and Singerman). Fluorescein angiogram with vitreous hemorrhage partially obscuring extensive neovascularization of the disk in a patient with thrombotic thrombocytopenic purpura when first seen by us.

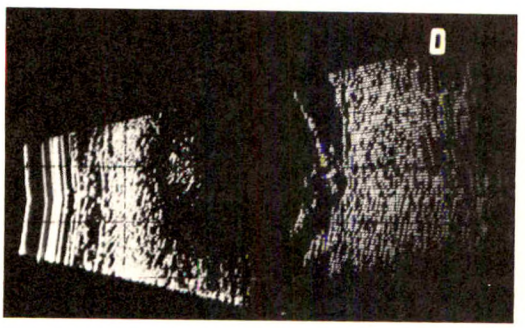

Fig. 2 (Lewellen and Singerman). B-scan of left eye. The probe was oriented vertically and allowed visualization of a retinal detachment extending nasally and temporally from the inferior margin of the disk. Similar views of the superior fundus showed no detachment.

sion reconfirmed the inferior retinal detachment previously partially noted at clinical examination. Additionally, a retinal break was noted at the 1:30 o'clock position between the ora serrata and the equator. No other breaks were seen. A small gutter of shallow retinal detachment extended peripherally from the 1:30 o'clock break to the inferior detachment.

The combined vitrectomy and scleral buckling approach allowed the identification of the superior retinal break that would not have been anticipated from the observable configuration of the retinal detachment. If we had buckled the inferior 180 degrees blindly, the procedure would have failed to re-attach the retina.

The patient tolerated the procedure well. Her retina was completely flat by the first postoperative day and has remained attached, with clear media (Figs. 3 and 4).

Discussion

The first case of thrombotic thrombocytopenic purpura was described in 1925 when Moschcowitz[1] reported an unusual clinical constellation associated with hyaline thrombi in the arterioles and capillaries of a young girl. This disease is a distinct clinical entity, characterized by the following five clinical signs: (1) thrombocytopenia; (2) microangiopathic hemolytic anemia; (3) fluctuating signs of neurologic dysfunction; (4) renal failure; and (5) fever. The pathologic findings of this disorder typically include the presence of platelet-fibrin thrombi in small arteries and arterioles of tissues throughout the body.

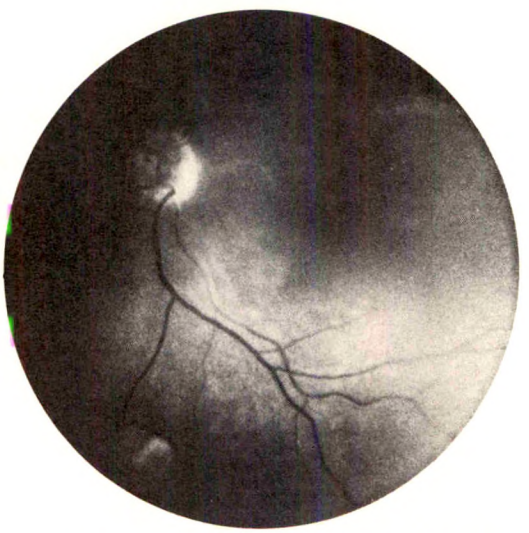

Fig. 3 (Lewellen and Singerman). A wide-angle photograph of this patient's left eye after vitrectomy.

Ocular involvement in this disease was reviewed by Percival[2,3] in 1970. The ocular findings included the following: exudative retinal detachment; choroidal hemorrhage; homonomous hemianopia; diplopia; anisocoria; papilledema; and retinal hemorrhage. Percival[3] described 47 patients with retinal hemorrhages, of

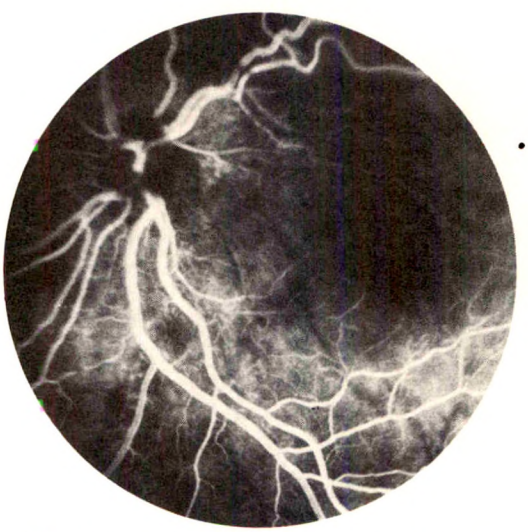

Fig. 4 (Lewellen and Singerman). Fluorescein angiogram of this patient's left eye after vitrectomy.

which 30 cases were attributed to either thrombocytopenia or retinal microangiopathy. There have been a few reports of retinal hemorrhages in patients with thrombotic thrombocytopenic purpura related to retinal veins. In 1966, Moorhead[4] suggested that such hemorrhages could be caused by thrombi in these vessels. A few years earlier, thrombosis of retinal vessels had been documented in a patient with this disease in the presence of verrucal vegetations of heart valves.[5] Such vegetations are present in up to 10% of patients with this disorder. Sludging of a branch of the retinal artery has also been reported in a patient with thrombotic thrombocytopenic purpura.[6] No retinal neovascularization was reported in any of these cases.

The mechanism of retinal neovascularization has been relatively well established. Little[7] states that viable retinal endothelium and retinal hypoxia must be present for retinal neovascularization to occur. Ischemia can result from changes in the blood constituents or changes in the blood vessels themselves.

We believe that thrombotic microangiopathic changes took place in the peripheral retinal microvasculature of our patient. The primary cause of these occlusions is presumed to be the formation of platelet-fibrin thrombi. Additionally, the increased fibrinogen during her hospitalization may have increased the ability of her erythrocytes to aggregate. The combination of these occlusive phenomena, anemia, and a low arterial PO_2 in our patient resulted in a sufficient hypoxic stimulus for neovascularization to occur.

In view of the physical findings and medical history, the optic atrophy observed in our patient may have resulted from any of three causes. According to Hayreh,[8] the prelaminar region of the optic nerve head is supplied mainly by the peripapillary choroidal vessels. The choroid itself is a prime site for occlusive phenomena in patients with thrombotic thrombocytopenic purpura. Thus, direct occlusion of the vessels of the optic nerve may have occurred. However, an electroretinogram was not available, which would have been helpful in differentiating retinal from optic nerve occlusive disease in our patient. An increase in intracranial pressure with secondary optic atrophy is another possibility in our patient as this condition existed during several weeks of her hospitalization. Additionally, vitamin B_{12} deficiency[9] may have played a role in the development of the optic atrophy observed.

It has been suggested that in diabetics, the presence of optic atrophy may be associated with a milder form of retinopathy than that found in the presence of a normal disk. Aiello and associates[10] reported that in diabetic patients with unilateral optic atrophy and bilateral retinopathy, the vessel changes are more extensive in the eye without the atrophic changes. In our patient, however, optic atrophy was associated with florid neovascularization in the ipsilateral eye.

Summary

A 33-year-old woman had thrombotic thrombocytopenic purpura. She developed optic atrophy and bilateral neovascularization of the disk with extensive vitreous hemorrhage that progressed to traction and rhegmatogenous retinal detachment.

Acknowledgment

Paul Mahar, M.D., referred this patient to us.

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Ophthalmic miniature

Ophthalmic Photography—Some advance has been made in the method employed to obtain photographs of the fundus oculi of animals, by Dr. Henry D. Noyes, of New York, Dr. A. M. Roseburgh, of Toronto, Canada, and we believe, also, by Dr. Liebreich. The fundus of the human eye has not yet been photographed, yet we cannot doubt but that it will be done. It has been suggested that the quality of the light has not, perhaps, been sufficiently studied. That is, is there not some form of illumination to which the plate, but not the eye, is particularly sensitive? The photographist and the physiologist must combine their knowledge and efforts. It will certainly be a great gain to be able to photograph important cases of internal disease of the globe, for now the difficulty and expense of producing a colored lithograph, to represent even faintly morbid changes, is very great, and we all know how impossible it is to intelligibly describe what we see.

Trans. Am. Ophthalmol Soc. 3:5, 1866

CLOTH-PARTICLE RETINAL EMBOLI FROM ARTIFICIAL CARDIAC VALVES

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The introduction of cloth-covered artificial cardiac valves in 1966 reduced the incidence of thromboembolism after valve replacement surgery to approximately 5% in patients who receive adequate anticoagulation.[1] However, cloth-covered valves may cause serious additional problems, which require important therapeutic decisions. Postoperative hemolytic anemia, systemic cloth-particle embolism, and valvular insufficiency led to reoperation in 2.5% of 204 patients in one recent series.[2]

The first report of cloth wear that caused embolism and required valve replacement involved the cerebral circulation of a patient with an aortic prosthesis.[3] Although transient loss of vision has been reported with a cloth-covered Starr-Edwards mitral valve,[2] to the best of our knowledge, there have been no reported instances of permanent visual deficit related to the use of cloth-covered artificial valves. We describe two patients with retinal emboli caused by such prostheses.

CASE REPORTS

Case 1—A 28-year-old woman underwent closed mitral commissurotomy for rheumatic heart disease here in January 1962. Postoperatively, a stable course was maintained with warfarin therapy until 1966, when intermittent diuretic therapy for pedal edema was instituted. By January 1970, a gradual onset of dyspnea on exertion and increasing pedal edema required daily doses of furosemide and digoxin. Recurrent mitral stenosis of moderate degree with congestive heart failure was diagnosed. A 3M Starr-Edwards cloth-covered mitral ball valve prosthesis was implanted in May 1970. The patient clinically improved and received warfarin therapy until November 1970.

On March 10, 1971, the patient suffered a sudden, painless inferior field loss of her left eye. Several amaurotic episodes of similar nature preceded this by several weeks. She was not receiving anticoagulant therapy. Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/600 (20/2,000). Examination of the right eye showed a minute crystalline embolus in the far peripheral branch of a superior macular arteriole. The left eye showed a recent embolic occlusion of the superior bifurcation of the central retinal artery with ischemic edema of the retina. Several cotton-wool patches were seen near the disk at the 12 and 1 o'clock positions (Fig. 1, left). Warfarin therapy was resumed, and the patient was asymptomatic for two months.

In May 1971, visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/7.5 (20/25). The embolus in the right eye was gone, and the left eye showed sector disk pallor and sheathing of the occluded superior temporal arteriole. In July 1971, a scotoma developed in the temporal field of the right eye. Visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/120 (20/400). A small embolus was lodged at the first bifurcation of the superior nasal artery of the right eye, with fragmentation of the distal blood column (Fig. 1, right). The prothrombin time was 51 seconds. One week later the embolus was gone. The left eye was unchanged. Warfarin therapy was continued.

On Feb. 22, 1973, the patient was re-examined. In the fall of 1971, approximately four months after she was last seen, she had dysphasia and agraphia that lasted one week, but she had no neurologic residual. She also had several brief amaurotic episodes of her left eye and was treated with aspirin by her primary physician. Visual acuity was R.E. 6/6 (20/20) and L.E.: 6/600 (20/2,000). The right eye was normal on examination, and the left eye had sector disk pallor again. Visual fields were normal in the right eye, but an absolute inferior arcuate defect involving fixation was present in the left eye (Fig. 2). Her primary physican instituted therapy with dipyridamole in March 1973 for symptoms of brief visual blur.

She had no further symptoms until Aug. 21, 1973, when a five-minute episode of amaurosis of the right eye occurred. On Sept. 7, 1973, visual acuity was R.E.: 6/120 (20/400) and L.E.: counting fingers. There was an occlusion of the inferior bifurcation of

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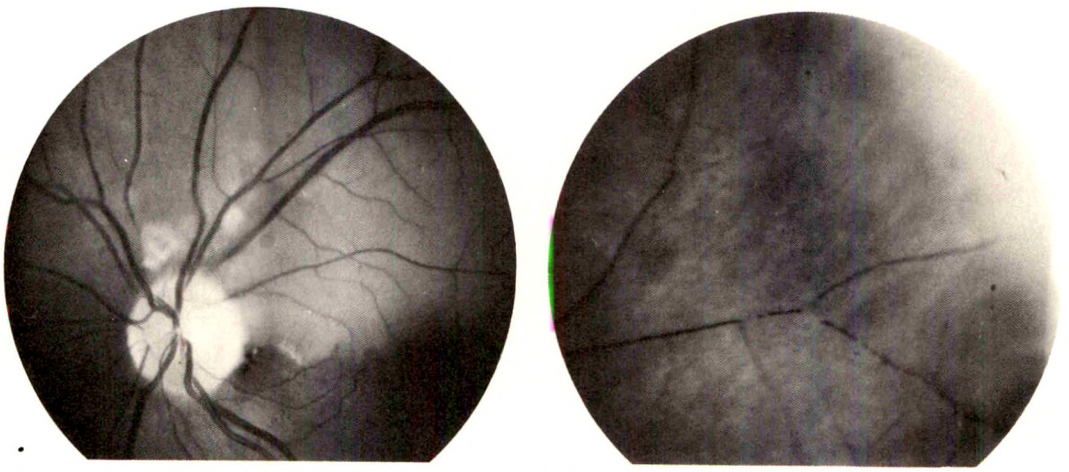

Fig. 1 (Rush, Kearns, and Danielson). Case 1. Left, Left eye, March 10, 1971. Superior temporal branch artery is occluded, causing ischemic retinal edema two days after onset. Occlusion was probably caused by fibrin-platelet embolus. Right, Right eye, July 9, 1971. Embolus lodged at first bifurcation of superior nasal arteriole, and fluffy gray emboli line the inferior branch arteriole.

the central retinal artery of the right eye, with residual ischemic edema of the retina. No embolus was seen. The left eye showed moderate disk pallor. She was asymptomatic until April 11, 1977, when pain developed and no radial pulses could be detected in her left arm. Occlusion of the left axillary artery was shown on angiography, and an emergency embolectomy was performed. Because of showers of cerebral, ocular, and systemic emboli, the Starr-Edwards valve was replaced with a Hancock prosthesis on April 27, 1977. At surgery, the damaged valve showed fragmentation and shredding of the cloth covering, with many areas of cloth loss. Two years have elasped without further ocular or neurologic complaints, but the patient's vision remains poor.

Case 2—A 52-year-old man was first seen here in 1969, when mitral regurgitation was diagnosed. In December 1973, furosemide and digoxin therapy was instituted for congestive heart failure. Fluoroscopy and cardiac catheterization showed severe pulmonary hypertension, and mitral valve replacement, using an M-32 cloth-covered Braunwald-Cutter valve, was performed on Dec. 17, 1973.

Postoperatively, the patient did well until January 1979, when continuous blurred vision of the right eye for two weeks prompted ocular examination. Visual acuity was 6/6 (20/20) in both eyes, and vitreous floaters were seen in the right eye. Results of the remainder of the ocular examination were unremarkable.

He returned in three weeks because of increased blurring of vision in his right eye, although his visual acuity was still 6/6 (20/20) in both eyes. There was a small hemorrhage on the right optic disk, as well as a hemorrhage along the superior temporal vein. The superior and inferior temporal arteries showed what appeared to be yellow exudates scattered on their surfaces. The erythrocyte sedimentation rate, antinuclear antibody titer, and the lupus erythematosus cell test were normal. Rheumatoid factor in a titer of less than 1:20 was present. Vasculitis was diagnosed, and 40 mg of prednisone daily was initiated on Jan. 10, 1979. On Feb. 12, 1979, the patient was reexamined. Visual acuity was normal in each eye, but the right eye showed multiple retinal emboli. Most of these were fuzzy, corresponding to what initially were believed to be exudates, but small shiny emboli were also visible in the superior nasal artery (Fig. 3). In the absence of severe visual loss or other embolic manifestations, surgical replacement of the prosthetic valve was deferred.

Discussion

Since the first Starr-Edwards prosthesis was implanted clinically in 1960, several modifications have been made to reduce the incidence of postoperative embolism. Early cloth-covered models of the Starr-Edwards ball valve used cloth-covered struts of polypropylene over Teflon and a cage seat of stellite metal covered by polypropylene over Teflon. The cloth-covered Braunwald-Cutter

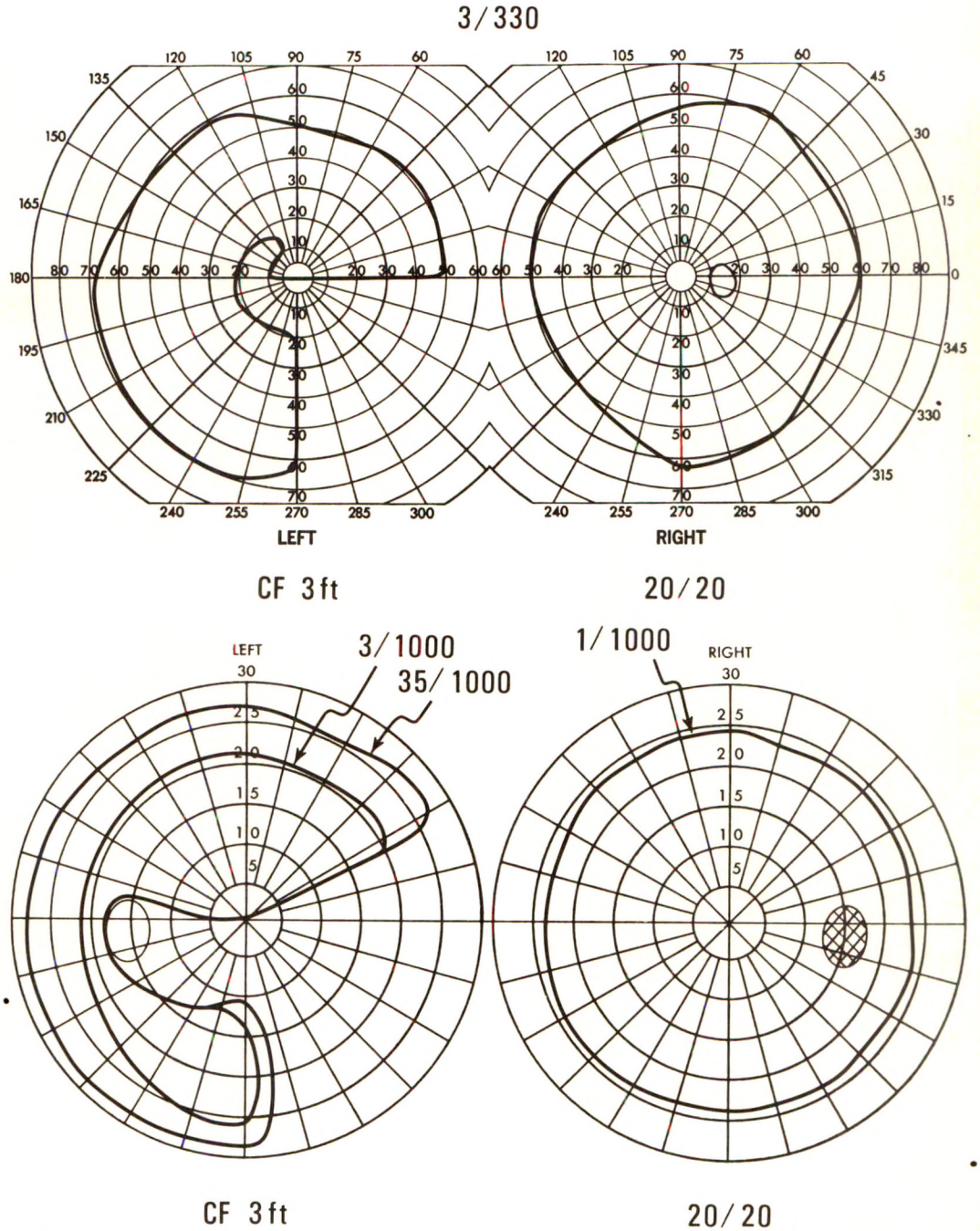

Fig. 2 (Rush, Kearns, and Danielson). Case 1. Feb. 1, 1973. Top, Perimetry shows inferior arcuate defect breaking out into inferior nasal periphery. Bottom, Tangent screen fields show inferior arcuate defect on left, involving fixation.

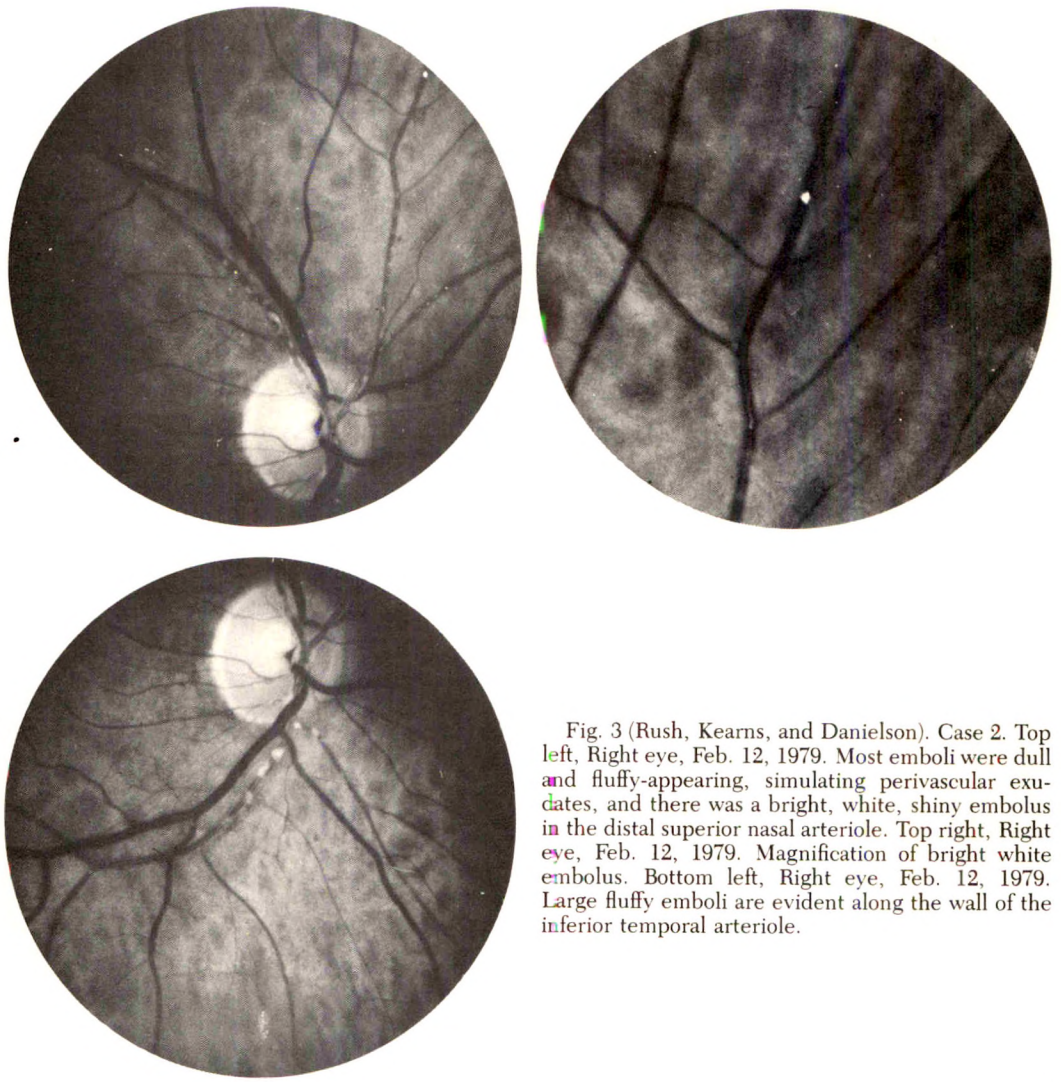

Fig. 3 (Rush, Kearns, and Danielson). Case 2. Top left, Right eye, Feb. 12, 1979. Most emboli were dull and fluffy-appearing, simulating perivascular exudates, and there was a bright, white, shiny embolus in the distal superior nasal arteriole. Top right, Right eye, Feb. 12, 1979. Magnification of bright white embolus. Bottom left, Right eye, Feb. 12, 1979. Large fluffy emboli are evident along the wall of the inferior temporal arteriole.

valve had a thin knit Dacron tubing over the struts and a single layer of polypropylene mesh over the seat.

The introduction of these cloth-covered cardiac valves reduced the overall incidence of thromboembolism to between 0 and 7%.[1,2,4-6] However, postoperative hemolytic anemia, systemic embolism, and valve insufficiency necessitated re-operation in 2.5% of patients with these cardiac prostheses.[2] Embolic events occur primarily as transient ischemic attacks or stroke and are more frequent with worn cloth-covered aortic valve prostheses.[2]

The first report of cerebral embolism caused by cloth wear of a Starr-Edwards prosthesis involved a 51-year-old man who suffered a right hemisphere stroke 13 months after implantation of an aortic valve.[3] Two later episodes of cerebral transient ischemic attacks, despite anticoagulation, required replacement of the prosthesis, which had severely fragment-

ed cloth. His subsequent course was uneventful.

Multiple episodes of amaurosis fugax in a 40-year-old man necessitated reoperation seven years after implantation of an artificial mitral valve.[2] No emboli were present ophthalmoscopically. At surgery, cloth loss was approximately 50%, and loose threads were found in the valve ring, with no thrombus formation.

Our two patients sustained visual symptoms months to years after the implantation of a cloth-covered mitral valve prosthesis. Embolic eye disease in each patient occurred only after surgical correction of mitral valve disease, which was present eight and four years before valve implantation.

In our first patient, bilateral emboli were seen ten months after surgery. Because anticoagulant therapy was not being given at the time, the emboli may have been thrombotic in origin, arising from the valve. However, subsequent emboli during a three-year period caused severe bilateral visual loss despite therapeutic anticoagulation. The likely source of emboli is the cloth covering of the prosthesis, because cloth remnants were seen at surgery. According to Shah and associates,[2] emboli occurring late during the postoperative course of patients adequately treated with anticoagulents is virtually prima facie evidence of cloth wear.

Our second patient had no systemic embolism until five years after implantation of a cloth-covered mitral valve. Late wear of cloth has been reported with Dacron-covered Braunwald-Cutter valves.[6] Retinal emboli of varying shapes were present in our patient. The bright refractile particles in the superior nasal artery may represent Dacron, a synthetic material similar to Teflon that is refractile in histopathologic sections of infarcted tissue.[7] The fluffy emboli resembling exudates on the vessel walls may be polypropylene.

We attempted experimentally to reproduce embolization of prosthetic valve material that was mechanically fragmented to between 50 and 100 μ and injected into the internal carotid arteries of an adult rhesus monkey. We were unsuccessful in showing retinal emboli, and speculate that the bolus injection of fragmented Teflon and Dacron does not cause the same effect of gradual disintegration and continuous embolization of a prosthetic cardiac valve that may occur in the clinical patient.

The only previous report of prosthetic valve emboli to the eye that we could find involved an early model of the Starr-Edwards aortic valve that had a silicone rubber ball and no cloth covering.[8] Bilateral retinal emboli were visible ophthalmoscopically as "little white dots" and caused no visual deficit in either eye. Visual acuity was 6/6 (20/20).

Unlike all patients described previously, our patients showed significant visual symptoms presumed to be caused by prosthetic valve emboli. If visual symptoms occur months to years after implantation of a cloth-covered cardiac prosthesis in a patient treated with anticoagulents, careful ophthalmoscopic examination may show retinal emboli. Evidence of unusual embolization supports the diagnosis of valve dysfunction. Permanent visual loss may be prevented if the valve is replaced.

Summary

Two patients with prosthetic mitral valves had ocular complications. A 28-year-old woman suffered recurrent episodes of bilateral retinal embolization and consequent loss of useful vision over a period of two years despite therapeutic anticoagulation. Replacement of the valve was followed by cessation of the embolization. A 52-year-old man noted the abrupt onset of blurred vision in his right eye. Visual acuity was 6/6 (20/20)

bilaterally, but the right eye had many retinal emboli of varying shapes. Both patients had long-standing mitral valve disease, but ocular symptoms developed only after the implantation of a cloth-covered mitral valve prosthesis.

To the best of our knowledge, retinal emboli from cloth-covered cardiac valve prostheses have not been previously reported. Patients with such prostheses and ocular complaints who have adequate anticoagulation therapy should be carefully examined for retinal emboli. If emboli are present, valve dysfunction is possible and valve replacement may be necessary.

ACKNOWLEDGMENTS

Michael P. Kaye, M.D., and Paul E. Zollman, D.V.M., assisted in the experiment to reproduce cloth-particle emboli in the rhesus monkey.

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RETINAL AND CHOROIDAL MICROVASCULAR EMBOLISM AFTER INTRANASAL CORTICOSTEROID INJECTION

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There is an association between methylprednisolone acetate suspension (Depo-Medrol) injection in the nose and embolization of the retinal and choroidal circulation by particles of the drug suspension. We report two cases that show this mechanism.

CASE REPORTS

Case 1—A 34-year-old woman suffered from allergic rhinitis and asthma and had had several surgical procedures for removal of nasal polyps. In May 1977 she had an endonasal procedure that consisted of a septoplasty, an intranasal ethmoidectomy, and the removal of many polyps. At the end of the procedure 1.5 ml of methylprednisolone acetate suspension was injected into the upper structures of the ethmoid and adjacent septum posteriorly on both sides. The procedure was done under general anesthesia and was uneventful. Her blood pressure was 104/62 mm Hg preoperatively and 90/70 mm Hg postoperatively.

On awakening from the anesthetic she immediately noted marked loss of vision in the right eye. Her visual acuity in the right eye was recorded as hand movements at 15 cm. The right pupil was dilated and fixed. On ophthalmoscopic examination nine hours after surgery she had many white emboli in the retinal and choroidal vessels on the right side (Fig. 1). The retina showed marked ischemic swelling and a cherry red spot at the macula. The disk was pale.

She was given Carbogen (8% CO_2, 90% oxygen) to inhale and a right stellate ganglion block was performed. No local retinal vascular response to these measures could be identified.

During the next 24 hours her visual symptoms remained unchanged. On ophthalmoscopy the embolic material was found to be packed into the smaller terminal arterioles in the retina and was more aggregated in the choroid. By 36 hours there was less material visible in both of the circulations. In 72 hours it was difficult to see any remaining emboli within the choroidal vessels. There was, however, significant retinal opacification. Three days after the episode her visual acuity had improved to hand movements at 1 meter. Retinal swelling was marked and there were many white emboli in the smaller retinal arterioles. The choroidal deposits were obscured by the retinal opacity.

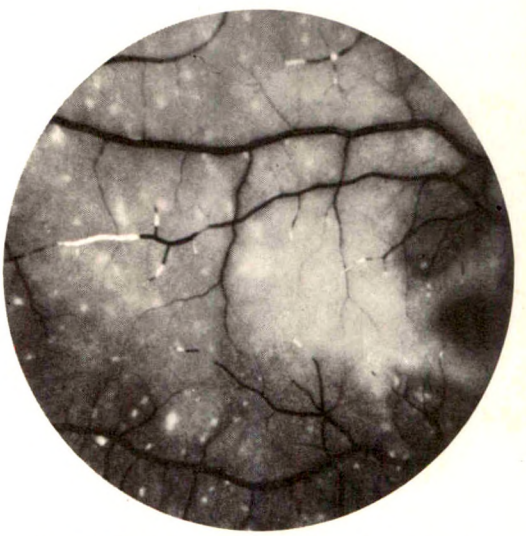

Fig. 1. (Whiteman, Rosen, and Pinkerton). Case 1. Right fundus photograph 24 hours after intranasal injection showing embolic material in terminal arterioles and clumped in the choroidal circulation. Retinal and macular edema visible with cherry-red spot to the right.

Three weeks later visual acuity in the right eye was counting fingers at 15 cm. There was loss of direct response to light in the right eye. The right disk was pale with some scattered subretinal pigmentation at the posterior pole. Some sheathing of a small arteriole above the macula was evident. All emboli had disappeared.

In three months the only significant findings were marked disk pallor on the right and some scattered pigmentation at the posterior pole. Visual acuity had not improved.

Case 2—A 23-year-old man had a submucous

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resection and turbinate resection in 1971 for chronic allergic rhinitis and sinusitis. In August 1973 he had a repeat bilateral partial turbinate resection with injection of methylprednisolone acetate suspension into the congested turbinate area. On awakening from general anesthesia he complained of reduced vision in his right eye.

On examination the next day, visual acuity was R.E.: 6/30 (20/100) and a central scotoma was charted. He had numerous emboli in the terminal branches of the retinal arterioles. These were white and filled a considerable length of the terminal arterioles. Retinal swelling was marked at the posterior pole. Fundus photographs were taken at this time 24 hours after the injection (Fig. 2).

On the following day the number of emboli had decreased and in two more days all the emboli had disappeared. Visual acuity in six weeks had improved to 6/21 (20/70). In six months visual acuity had further improved to 6/18- (20/60-).

Discussion

These two cases show the occurrence of retinal and choroidal vascular embolism subsequent to the injection of methylprednisolone acetate suspension into the nasal mucosa in the ethmoidal area for the control of chronic inflammatory changes there. The embolism occurs at the time of injection, and depending on its volume, all evidence of it may have disappeared in three to four days. Thus, the identification of the cause of the visual loss may be missed because of the rapid clearance of the emboli from the retinal and choroidal circulation.

The proposed route of the embolization is shown in Figure 3. Presumably, there is retrograde injection along the anterior and posterior ethmoidal arteries to the ophthalmic artery where the material is distributed to the central retinal artery and the short posterior ciliary arteries. The route by which the material enters the ethmoidal arteries remains uncertain. Otolaryngologists believe that the chance of direct injection into the anterior ethmoidal artery is small. An alternative suggestion is that the placement of the material under pressure into a chronically inflamed tissue with a sinus-

Fig. 2 (Whiteman, Rosen, and Pinkerton). Case 2. Right fundus 24 hours after injection shows white embolic material in terminal arterioles and extensive retinal and macular edema.

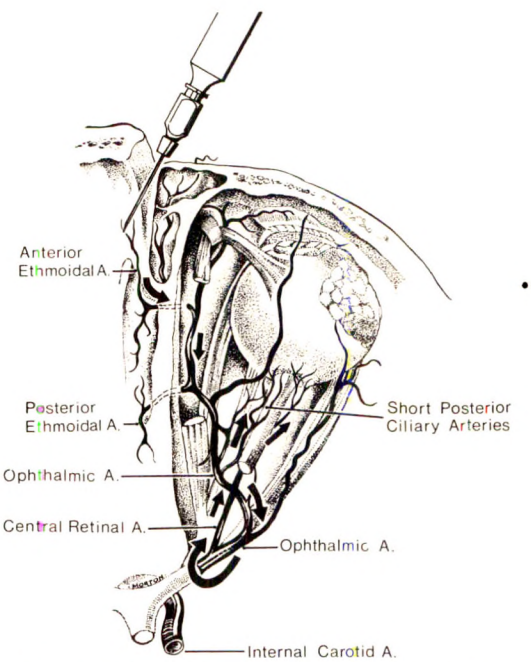

Fig. 3. (Whiteman, Rosen, and Pinkerton). Proposed route of retrograde flow in peripheral ophthalmic artery supply.

oidal vascular system may produce easier accesss to the supplying arteries. Both the anterior and posterior ethmoidal arteries supply the nasal mucosa in the area where these injections are made. Methylprednisolone acetate flows easily through a No. 22 gauge needle and excessive pressure is not required for this injection.

Seventy-five percent of methylprednisolone acetate particles are 10 nm or less in size and the terminal arteriolar diameter in the retina and choroid is 8 to 15 nm so that the relative sizes are compatible.

Byers[1] noted the wide source of emboli to the ophthalmic arterial system, cases being reported after particulate injection in the lips, face, scalp, and tonsillar fossa. Ellis[2] described occlusion of the central retinal artery after retrobulbar corticosteroid injection and noted emboli that he took to be the corticosteroid in the retinal arterioles. He hypothesized that the route of the emboli was by retrograde flow from a small branch of the central retinal artery to its main vessel.

From the case reports it is evident that injections of particulate material should be avoided in the ethmoidal and tonsillar areas, because the particles may form significant emboli in the end circulations of the retina and the choroid with resultant irreversible retinal, choroidal, and optic nerve head ischemia. In the circumstances where this therapy is necessary, Byers[1] suggested that it be accompanied by a topical decongestant.

Summary

Two patients had uniocular visual loss after methylprednisolone acetate (Depo-Medrol) injection for control of chronic inflammatory conditions in the nose. The cause of the visual loss was embolic retinal and choroidal vascular occlusion. The emboli were presumably aggregates of microcrystals of methylprednisolone acetate.

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SUBCONJUNCTIVAL CORTICOSTEROID THERAPY COMPLICATED BY HYPERINFECTIVE STRONGYLOIDIASIS

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Subconjunctival corticosteroids have not been widely recognized for their systemic effects. Recently, such treatment has been shown to suppress adrenal function like other systemic corticosteroid therapy.[1] Infections and other complications of chronic high dose corticosteroid therapy have been recognized for several years. However, most ophthalmologists have neither seen such complications nor been aware of them in relationship to subconjunctivally injected corticosteroids. To the best of our knowledge, this is the first ophthalmic report of invasive strongyloidiasis developing in a patient after receiving subconjunctivally injected corticosteroids, although it has been reported briefly elsewhere.[2]

CASE REPORT

A 57-year-old man was injured in the right eye two years earlier by limestone dust, which resulted in decreased vision. In early 1973 he sought care because of three weeks of severe pain in his right eye. A central corneal ulcer was diagnosed during admission to a local hospital. He complained of headaches. Results of a physical examination were normal except for the eye and his blood pressure was 170/100 mm Hg. Gram stain of material from the corneal ulcer showed gram-positive diplococci and neutrophils. Hemoglobin was 15.7 g/100 ml; white blood cell count was 8,600/mm^3; and differential white blood cell count included 10% eosinophils. Local and systemic antimicrobial therapy lessened the inflammatory exudate and relieved pain, but the corneal ulcer deepened. This prompted his transfer to a tertiary care hospital, ophthalmology service. The white blood cell count was 12,500/mm^3; but a differential white blood cell count was not recorded.

The eye was treated topically with cyclopentolate HCl, phenylephrine HCl, gentamicin, prednisolone acetate, and scopalamine hydrobromide for nine days. A penetrating keratoplasty was performed on the tenth day. On day 14 the patient's pupil could not be dilated; therefore, 4 to 8 mg of dexamethasone injected subconjunctivally daily was begun and continued for six weeks. Topically administered corticosteroids and gentamicin were used concurrently and continued after the dexamethasone was stopped. Because of anorexia and debilitation, a medical consultation was obtained on the 58th hospital day. The patient vomited two-day-old food during this examination, and shortly thereafter developed a large upper gastrointestinal hemorrhage. The patient was treated for peptic ulcer disease. A large gastric ulcer and gastritis were found at endoscopy. Treatment for the ulcer did not resolve the symptoms of anorexia and gastric atony or reverse further deterioration. Each time the nasogastric tube was removed, gastric dilatation recurred. Constipation was attributed partially to painful hemorrhoids. A fever developed and was caused by *Serratia marcescens* bacteremia. White blood cell count was 15,700/mm^3 with 19% eosinophils. Cerebrospinal fluid examination showed a pleocytosis of 1,050 cells/mm^3 of which 91% were neutrophils; the protein was increased to 73 mg/dl, but the glucose was normal. Microbiologic smears and cultures were negative. He received a course of chloramphenicol, penicillin, and gentamicin, administered intravenously, with resolution of the fever, bacteremia, and meningitis. However, his debilitation, gastric atony that resembled gastric outlet destruction, and eosinophilia persisted. Transient pulmonary infiltrates, a nonpruritic evanescent skin rash, and hepatomegaly were noted. Bone marrow examination showed a large increase in eosinophils and erythroid hypoplasia. Upper gastrointestinal and small bowel X-rays showed no ulcer or obstruction, but showed delayed gastric emptying, prolonged transit time, and small bowel mucosal changes consistent with edema and hypoalbuminemia.

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Repeat upper gastrointestinal endoscopy showed friability and three tiny superficial erosions, but no ulcer and no obstructing mass. Biopsies from the stomach and duodenum and duodenal fluid were obtained. The biopsies showed *Strongyloides* in the superficial mucosa; the duodenal aspirate and stool showed active *Strongyloides stercoralis* larvae. Treatment with six doses of 25 mg/kg of body weight of thiabendazole was given during three days' time. Because of the heavy infection and persistent eosinophilia and despite the absence of larvae in the stool, a repeat course of 25 mg/kg of body weight of thiabendazole, twice daily for two days, was administered four weeks later before discharge. In the interim, septic jugular vein thrombophlebitis with bacteremia caused by *Staphylococcus epidermidis* developed in the central venous line used for hyperalimentation. Removal of the line and cephalothin and gentamicin, administered intravenously, resolved the infection. Anemia and gastrointestinal function improved slowly. He was discharged after 120 days of hospitalization. One year later, a home visit in rural east Tennessee showed an overfilled outhouse to be the only toilet. Follow-up examination showed no *Strongyloides*, but new gastrointestinal symptoms were caused by *Giardia lamblia* and acid-fast bacilli were found in the patient's sputum. Vision in the right eye was not saved.

Discussion

Corticosteroids injected subconjunctivally are often used in clinical ophthalmology to supplement the therapeutic benefits of topically administered corticosteroids. Although such injections are intended as adjunctive local therapy, only recently has it been shown that such injections suppress adrenal function like other systemic corticosteroid therapy.[1] That such therapy also can result in severe complications of systemic corticosteroid therapy is not well recognized. Our patient had asymptomatic eosinophilia and developed hyperinvasive strongyloidiasis associated with peptic ulcer disease during and after six weeks of subconjunctivally administered dexamethasone in supraphysiologic doses.

Strongyloidiasis is an endemic upper intestinal infection that occurs in the tropics and subtropics, including the Southeastern United States. A higher prevalence is noted in regions where modern plumbing is unavailable[3] and in institutions,[4] including one in the Soviet Union,[5] where patients cannot or do not use toilets. The prevalence is unknown, but is widely assumed to exceed the symptomatic cases, which in turn exceed the diagnosed cases. Because asymptomatic cases of up to 40 years' duration are documented, the infection may cause few or no symptoms whatsoever.[6] The relative lack of sanitary facilities for human excrement at our patient's home probably was the reason for his original infection, presumably years earlier.

It is well established that corticosteroids systemically administered and certain other immune-altering drugs can change an asymptomatic intestinal *Strongyloides* infection into a symptomatic, hyperinfective, or fatal case.[7-12] Impaired gastrointestinal motility favors the same complication by permitting the intraintestinal maturation of rhabditiform larvae into filariform larvae, which autoinfect or hyperinfect the patient via the gastrointestinal tract,[13] the biliary tract,[14] or the perianal skin.[15] In this case, decreased gastrointestinal motility might represent both an effect of the strongyloidiasis, as previously reported in severe cases,[8,10-12,14,16,17] and a contributing cause of further auto- or hyperinfection. His decreased gastrointestinal motility was probably multifactorial and reflected prolonged bed rest, constipation related to painful hemorrhoids, decreased food intake, and the developing *Strongyloides* infection. Although symptomatic *Strongyloides* may resemble peptic ulcer disease,[18] our patient had both. *Strongyloides* usually causes diarrhea,[18] malabsorption, or both,[17] when it becomes symptomatic; none of these were seen in our patient. Additionally, because hyperinfective strongyloidiasis rarely occurs in the absence of immunosuppression or severe malnutrition, it served as a specif-

ic marker of immunosuppression in this patient.

The causal relationship between gastric peptic ulceration and corticosteroid therapy is a firmly established medical opinion.[19] However, in our patient many other processes were in themselves stressful; for example, the corneal ulcer and its treatment. The presence of a previously asymptomatic *Strongyloides* infection at least interacted with other influences to alter and damage the gastric and intestinal mucosa. Did the ulceration promote invasion by *Strongyloides* or did the massive *Strongyloides* infection directly damage the gastric mucosa and then further contribute to peptic ulceration by causing gastric atony, thus keeping the damaged mucosa awash in acid secretions? The sequence is unknown, but neither the *Strongyloides* nor the gastric peptic ulcer contributed to the resolution of the other process. The large gastric ulcer had healed under antacid therapy in the three weeks between endoscopic examinations, and the strongyloidiasis had worsened. The radiographic findings in our case, while nonspecific, have been described previously.[14,16]

The *Serratia marcescens* was introduced into his blood via damage to the gastrointestinal tract by the *Strongyloides* larvae. The coincidence of meningitis with the bacteremia suggests that culture-negative or early bacterial meningitis was beginning at the time of the cerebrospinal fluid examination. Severe strongyloidiasis often has been complicated seriously by the development of bacteremia and meningitis, most of which have been fatal.[20-24] Central nervous system dissemination of *Strongyloides* is an alternate explanation[2,11] of the cerebrospinal fluid abnormalities. Liver enlargement, transient pulmonary infiltrates, and the transient skin rashes seen in our patient are consistent with disseminated strongyloidiasis.

This case shows a specific danger of overuse of subconjunctivally injected corticosteroids. Additionally, data now available and not available at the time this person was under care show that concentrations of corticosteroids can be maintained at higher and almost constant concentrations in the cornea and anterior chamber by frequent topical applications than by once daily subconjunctival injection.[25] How does the ophthalmologist anticipate such an infectious complication of subconjunctival corticosteroid therapy? In this case, eosinophilia noted only at the local hospital was the clue to the diagnosis of strongyloidiasis. Just as the tuberculin skin test should be performed before starting corticosteroid therapy to decide if isoniazid treatment should accompany the use of corticosteroids, eosinophilia should be identified before the use of corticosteroids.

Summary

A 57-year-old man was treated for a corneal ulcer with a penetrating keratoplasty, followed by six weeks of a regimen of 4 to 8 mg of dexamethasone injected subconjunctivally daily. Before therapy, he was clinically well and 10% eosinophils were noted on his differential white blood cell count. He developed a gastric peptic ulcer with hemorrhage and severe strongyloidiasis of the stomach and duodenum that worsened as the ulcer responded to medical therapy. The strongyloidiasis resulted in physiologic gastric outlet obstruction by decreasing gastrointestinal motility. There was evidence of hyperinvasive and disseminated strongyloidiasis, complicated by meningitis and *Serratia marcescens* bacteremia. He survived and received thiabendazole treatment for strongyloidiasis, which was successful. Subconjunctival

corticosteroids caused a systemic effect that changed asymptomatic *Strongyloides* infection into hyperinvasive strongyloidiasis.

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PHOTOCOAGULATION OF ACTIVE TOXOPLASMIC RETINOCHOROIDITIS

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In 1952 Wilder[1] showed the importance of toxoplasmosis as a cause of focal posterior retinochoroiditis. Subsequent treatment of cases in which the macula is threatened has been predominantly medical.[2-5] Currently, the accepted method of treatment in these cases is a combination of pyrimethamine, sulfamethoxypyridazine and folinic acid administered orally or intramuscularly, or clindamycin and corticosteroids. These drugs have to be given for a period of weeks or months, and all have potentially serious systemic side effects.

Dobbie[6] used cryotherapy in the treatment of active retinochoroiditis, but because of the usual posterior location of the lesion, conjunctival incision under local or general anesthesia was required. Spalter and associates[7] reported photocoagulation applied around healed lesions to prevent recurrences in quiescent toxoplasmosis retinochoroidal scars. To the best of our knowledge, this is the first report of photocoagulation therapy in active toxoplasmic retinochoroiditis.

Five patients treated by one of us (R.J.B.) and at the Massachusetts Eye and Ear Infirmary are included in this report. Diagnosis was based on the following: (1) a typical, active, focal exudative retinochoroidal lesion with retinal edema; (2) absence of any other known specific cause; and (3) toxoplasmic serologic diagnostic studies. All patients were initially treated with a combination of systemic pyrimethamine, sulfadiazine, prednisone, and folinic acid. The retinal lesions were treated with photocoagulation only after they had failed to heal after several months of medical treatment as described previously.

CASE REPORTS

Case 1—A 23-year-old man was examined in August 1966 because of blurred vision in the left eye of several days' duration. Ophthalmic examination showed corrected visual acuity of R.E.: 6/4.5 (20/15) and L.E.: 6/30 (20/100), not improved by the pinhole test. Intraocular pressure (IOP) was R.E.: 15 mm Hg and L.E. 19 mm Hg. Biomicroscopy of the right eye showed no abnormality, and the fundus showed no evidence of active or healed retinochoroiditis. The left eye showed diffuse, fine keratic precipitates, 1+ flare, and ten cells per 0.1 × 2.0 mm beam in the anterior chamber. There were clumps of cells and pigment on the anterior capsule, and extensive infiltration of cells and pigment was noted in the vitreous cavity. Examination of the fundus showed two healed chorioretinal lesions at 9 and 10 o'clock near the equator. On the disk side of the 10 o'clock lesion an acute focus of retinochoroiditis was seen (Fig. 1). Skin tests for tuberculosis and toxoplasmosis, and the Hinton test were negative. Chest X-ray was normal. Daily doses of 100 mg of prednisone and local mydriatic treatment were prescribed. The prednisone was decreased to 80 mg every other day after one week.

The retinochoroiditis showed no signs of healing after four weeks on this regimen. Three intravenous typhoid treatments were given with significant febrile response, but with no effect on the retinal lesion. Sabin-Feldman dye test was then reported as positive with a titer of 1:64. The patient was given 25 mg of pyrimethamine three times daily, 500 mg of sulfadiazine four times daily, and continued receiving prednisone in variable dosages. These medications were continued for one year until September 1967.

On two occasions during this period, the lesion appeared to be inactive, but flared up again when the medications were decreased. Because of the chronicity and tendency of relapse of the lesion, photocoagulation treatment was advised. The Zeiss xenon photocoagulator was used with a setting of green I power, No. 1 iris diaphragm, and a 4.5-degree image field diaphragm. Twenty applications were placed on and around the active lesion at 10 o'clock.

The active retinochoroidal lesion was completely healed and inactive within three weeks (Fig. 2). At

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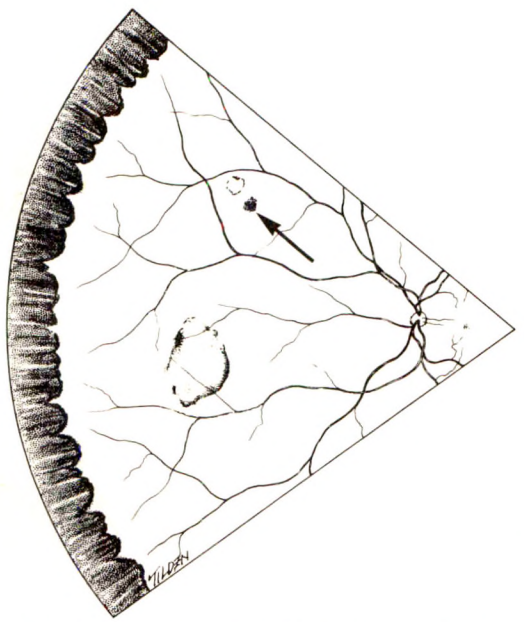

Fig. 1 (Ghartey and Brockhurst). Case 1. Fundus drawing shows a gray fluffy active focus of retinochoroiditis at 10 o'clock (arrow).

the last follow-up visit, seven years after the photocoagulation treatment, the retinochoroidal lesion was entirely inactive and the patient has retained visual acuity of 6/9 (20/30).

Case 2—A 28-year-old woman was examined in October 1972, because of blurred vision in the left eye of nine days' duration. Her medical history showed two similar episodes of blurred vision, one in 1967 and another in 1969, which subsided spontaneously.

Ophthalmic examination showed a normal right eye with visual acuity of 6/6 (20/20) without correction. Examination of the left eye showed visual acuity was limited to counting fingers at three feet. Biomicroscopy of the anterior segment showed marked flare and cells in the anterior chamber and numerous large keratic precipitates on the inferior half of the cornea. The vitreous body showed moderate flare and cells. Ophthalmoscopic examination of the left fundus showed an active focus of retinochoroiditis immediately temporal to the macula with edema of the fovea. Some pigmentation was present in the center of the active lesion. Skin tests for tuberculosis, toxoplasmosis, and histoplasmosis were negative. Hinton test and toxoplasmosis indirect hemagglutination test were negative and chest X-ray was normal.

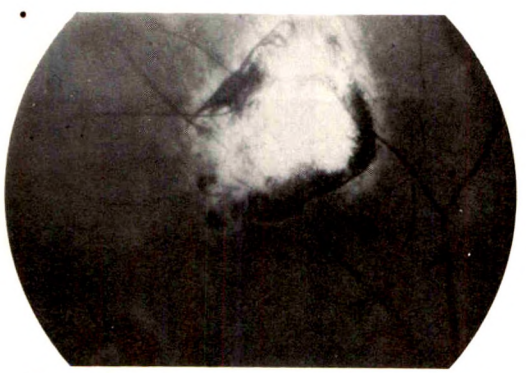

Fig. 2 (Ghartey and Brockhurst). Case 2. Fundus photograph of the healed inactive lesion three weeks after treatment.

The patient was treated with 100 mg of prednisone daily for one week and then 100 mg every other day, 25 mg of pyrimethamine three times daily, 500 mg of sulfadiazine four times daily, and 3 mg of folinic acid twice weekly. During the first month on this regimen, the lesion initially showed early signs of healing. However, during the following two months, the lesion did not show any sign of further resolution. Four months after the onset of treatment, central visual acuity improved to 6/6 (20/20), but immediately temporal to the macula a residual nidus of active retinochoroiditis persisted (Fig. 3).

The central nidus of the retinochoroiditis was treated with argon photocoagulation: 250-μ spot size, intensity of 200 mW and a duration of 0.5 second. The lesion was completely inactive two months after the treatment (Fig. 4). At the most recent follow-up visit nine months after treatment, the lesion was inactive, and central visual acuity was 6/6 (20/20).

Case 3—A 40-year-old woman was examined in May 1972, because of distortion of vision in the right eye. Her medical history showed that she had had three similar episodes during the previous three years with temporary remissions.

Visual acuity was 6/6 (20/20) in each eye. Intraocular pressure measured, L.E.: 12 mm Hg and R.E.: 14 mm Hg. Examination of the left eye showed no abnormality. Biomicroscopy of the anterior segment of the right eye was normal, but ophthalmoscopy showed slight vitreous haze and a chorioretinal scar temporal to the macula with a fluffy yellow-white active lesion at the superior edge of the scar. Skin tests for tuberculosis and histoplasmosis were negative. The Hinton test was nonreactive. Toxoplasmosis indirect hemagglutination test showed a 1:128 titer. The patient was treated with 100 mg of prednisone daily for one week and then 100 mg every other day, 25 mg of pyrimethamine three times daily, 500 mg of sulfadiazine four times daily, and 3 mg of folinic acid twice weekly. Improvement was noted during the next six weeks with a decrease in vitreous haze and a decrease in the size of the active fundus lesion. Because she complained of severe headaches and fatigue, pyrimethamine and sulfadiazine were discontinued, and prednisone was tapered over the next four weeks.

She was again examined in November 1972, because of marked blurring of vision of the right eye. Ophthalmic examination showed visual acuity of

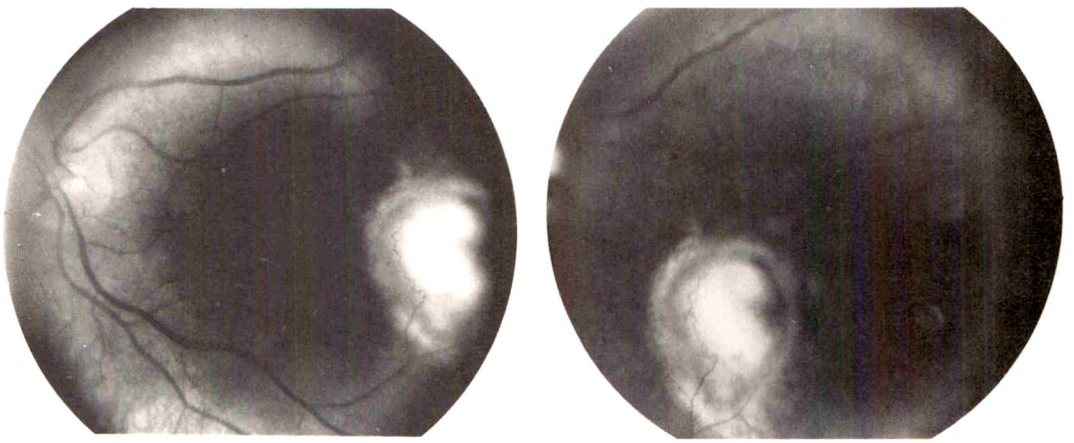

Fig. 3 (Ghartey and Brockhurst). Case 2. Fundus photographs of chronic focus of toxoplasmic retinochoroiditis close to the macula. (Note central elevated nidus.)

R.E.: 6/60 (20/200) L.E.: 6/6 (20/20). Intraocular pressure measured R.E.: 14mm Hg and L.E.: 10 mm Hg. Biomicroscopy of the right eye showed moderate flare and a few cells in the anterior chamber and anterior vitreous. Ophthalmoscopy showed three active foci of retinochoroiditis at the temporal margin of the original lesion. She was again given 100 mg of prednisone daily for one week and then 100 mg every other day, 25 mg of pyrimethamine three times daily, 500 mg of sulfadiazine four times daily, and 3 mg of folinic acid twice weekly.

By March 1973, the lesions were still active although she had been taking systemic medication for five months (Fig. 5). The active lesions were treated with xenon photocoagulation using green III power and a 3-degree spot size. She was maintained with systemic medications. The lesions healed in two areas but remained active at one site three weeks after treatment.

In May 1973, the patient was admitted to a mental hospital because of corticosteroid psychosis. Corticosteroids were omitted and the remaining active lesion was again treated with xenon photocoagulation on May 11, 1973. Ocular examination in July 1973, showed a healed chorioretinal scar and visual acuity of 6/6 (20/20) in the right eye (Fig. 6). When the patient was last examined four years after photocoagulation treatment, the lesion was healed and visual acuity was 6/6 (20/20).

Case 4—A 57-year-old man was examined in

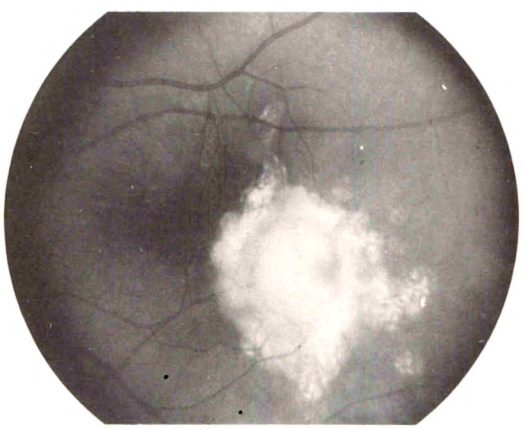

Fig. 4 (Ghartey and Brockhurst). Case 2. Two months after treatment the lesion is white and inactive.

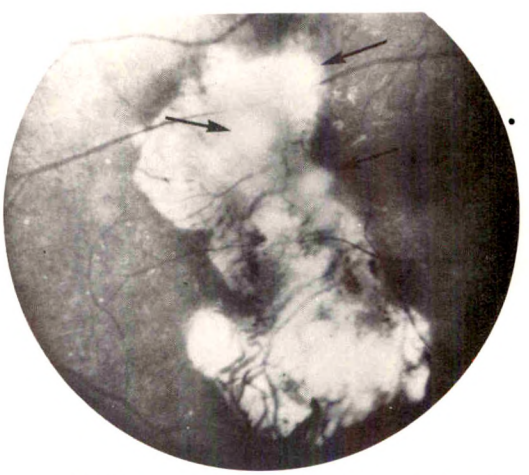

Fig. 5 (Ghartey and Brockhurst). Case 3. Fundus photograph shows large chorioretinal scar with three chronic active foci (arrows).

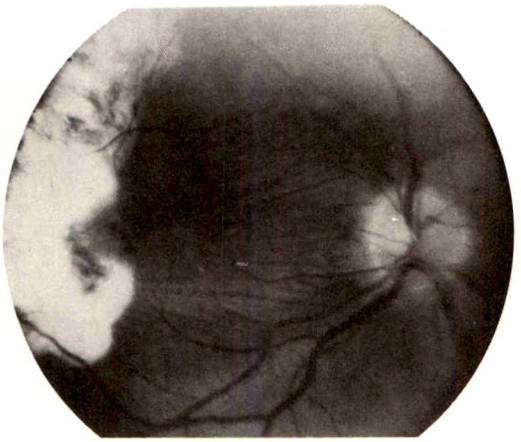

Fig. 6 (Ghartey and Brockhurst). Case 3. Fundus photograph shows atrophic inactive lesion.

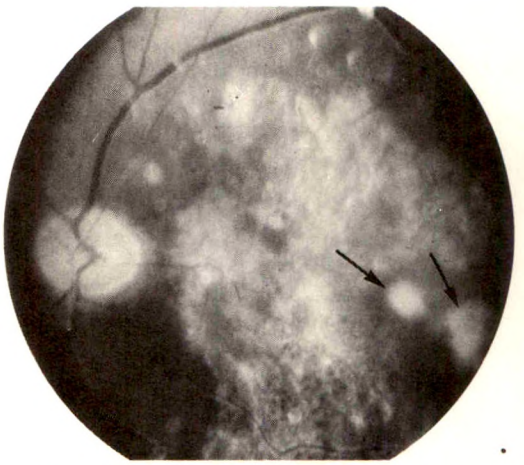

Fig. 7 (Ghartey and Brockhurst). Case 4. Fundus photograph shows focus of active retinochoroiditis (arrows).

October 1975. He complained of blurred vision in the left eye, which had been present for three years. Before his visit, he had been treated with systemic corticosteroids, but this was discontinued because of abdominal pain and fluid retention.

Corrected visual acuity measured R.E.: 6/7.5 (20/25) and L.E.: hand movements at six feet. Intraocular pressure was R.E.: 32 mm Hg and L.E.: 27 mm Hg. Biomicroscopy showed nuclear sclerosis and early posterior cortical cataract in the right eye. The left eye showed fine cells on the endothelial surface, a few cells on the anterior lens capsule, and slight nuclear and posterior cortical opacities. The vitreous was detached with many hyaloid precipitates.

Ophthalmoscopy of the right eye showed a slight pigment atrophy above the macula and diffuse chorioretinal atrophy along the ora serrata inferiorly. In the left eye the view was hazy, and old chorioretinal scars were seen in the periphery at 6, 9, and 12 o'clock. An active lesion involving the macula approximately ten disk diameters in size was noted at the posterior pole.

A skin test for tuberculosis was negative, chest X-ray was normal, and a blood Hinton test was negative. Toxoplasmosis indirect hemagglutination test was positive with 1:16384 titer.

He was treated with 100 mg of systemic prednisone every other day, 25 mg of pyrimethamine three times daily, 500 mg of sulfadiazine four times daily, and 3 mg of folinic acid administered intramuscularly twice weekly. After two months the precipitates on the detached posterior hyaloid of the left eye had cleared, and the vitreous became clearer. The retinochoroiditis appeared to be healing, but two small central nuclei in the lesion just temporal to the macula remained active (Fig. 7). His IOP increased to R.E.: 40 mm Hg and L.E.: 30 mm Hg. The prednisone was gradually tapered, but pilocarpine and epinephrine 1% eyedrops were continued in both eyes.

The retinochoroiditis showed increased activity and the vitreous opacities increased. Systemic prednisone was resumed until the vitreous cleared, and xenon arc photocoagulation of the lesions was performed in May 1976, using the red III intensity, a duration of two seconds, 4.5-degree field size, and 31 applications. Because of lens and vitreous opacities, it was not possible to obtain effective reaction.

During the next month, the retinochoroiditis decreased in size but remained active. He developed a high blood glucose level, corticosteroids were omitted and the lesion was re-treated with surgical diathermy and cryopexy, as further light coagulation would not be effective because of lens and vitreous opacities. This treatment was performed in July 1976, and the lesion healed within one month.

On his last examination in November 1977, the lesion appeared quiescent, and visual acuity had improved to counting fingers at two feet. The IOP was 18 mm Hg in both eyes with pilocarpine therapy. The lens opacities had increased and precluded satisfactory photography.

Case 5—An 18-year-old man was examined in November 1968, because of loss of central vision in the left eye of three days' duration. Retinochoroiditis had been diagnosed by his ophthalmologist. The patient was taking prednisone.

Ophthalmic examination showed a normal right eye with visual acuity of 6/6 (20/20). The left eye showed best corrected visual acuity of 6/60 (20/200). Biomicroscopy showed large amounts of cells in the anterior chamber and hazy vitreous. Ophthalmoscopic examination of the left eye showed three small active sites of retinochoroiditis involving the macula and paramacular region.

A skin test for tuberculosis and histoplasmosis was negative, X-rays of the chest, sinuses, and upper

teeth were normal, and blood Hinton test was negative. He was treated with 50 mg of prednisone for the next ten days. The prednisone was gradually discontinued during the following two weeks because his visual acuity had improved to 6/21 (20/70) with correction, and the lesion had become inactive.

Three years later in September 1971, he was again seen because of blurred vision in the left eye. Visual acuity in the left eye was 6/60 (20/200), and IOP was 32 mm Hg (Schiøtz). The fundus showed an active retinochoroiditis at the inferior edge of the old chorioretinal scar. Toxoplasmosis indirect hemagglutination titer was positive with 1:256 titer. He was treated with 100 mg of prednisone daily for one week and then 100 mg every other day for another week. The retinochoroiditis showed signs of healing and the prednisone was gradually discontinued. Additionally, he was treated with 250 mg of acetazolamide four times daily. The lesion healed within two months, ocular pressure was normal, and the medications were discontinued.

He had another recurrence of retinochoroiditis in the summer of 1973 while in Germany and was treated with prednisone and pyrimethamine. The lesion healed within one month, but he had to be hospitalized because of severe weakness. Another relapse occurred in May 1976, and he responded to prednisone treatment. In January 1977, he had another attack of retinochoroiditis that responded within three months to treatment with 300 mg of clindamycin four times daily and variable dosages of prednisone (100 mg to 40 mg) every other day. He had a relapse at the same focus in May 1977 (Fig. 8), and was again treated with prednisone and clindamycin. The retinochoroiditis was more extensive after one month (Fig. 9) and the patient was emotionally upset. He had had three attacks of retinochoroiditis within a period of one year and had been treated almost continously with systemic medication with no permanent response. Photocoagulation was, therefore, recommended.

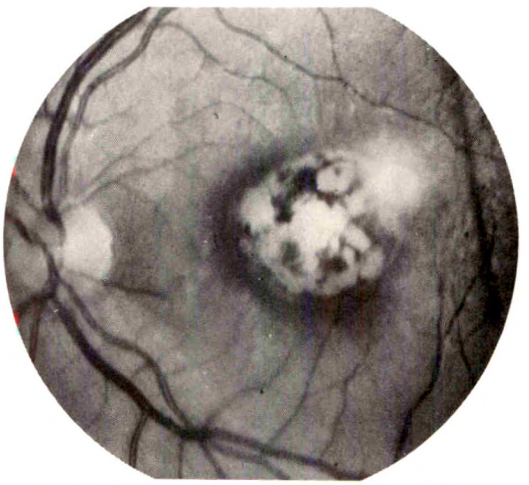

Fig. 8 (Ghartey and Brockhurst). Case 5. Fundus photograph shows active focus of retinochoroiditis at the temporal edge of previous retinochoroidal scar.

Argon laser photocoagulation treatment was performed in June 1977. A total of 74 applications were made using 500-μ spot size, a duration of 0.2 second, and a power of 250 to 350 mW (Fig. 10). The retinochoroiditis healed within three weeks. On his last examination two years after treatment, the lesion appeared inactive and visual acuity had improved to 6/21 (20/70) in the left eye (Fig. 11).

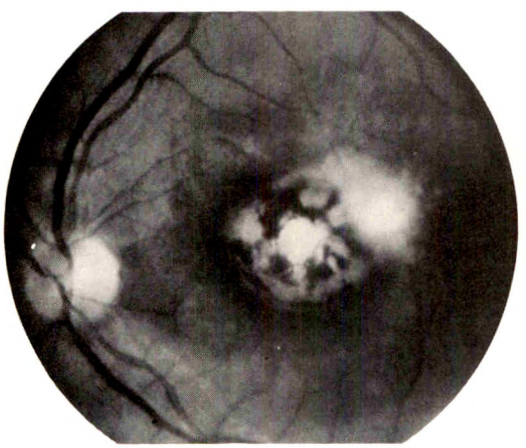

Fig. 9 (Ghartey and Brockhurst). Case 5. One month later, the lesion appears more extensive and more elevated.

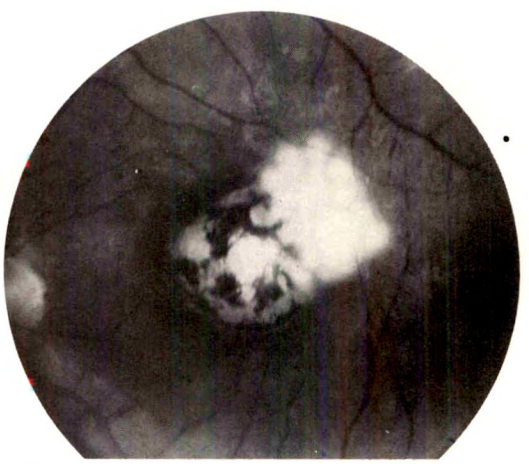

Fig. 10 (Ghartey and Brockhurst). Case 5. Fundus photograph immediately after argon laser photocoagulation treatment.

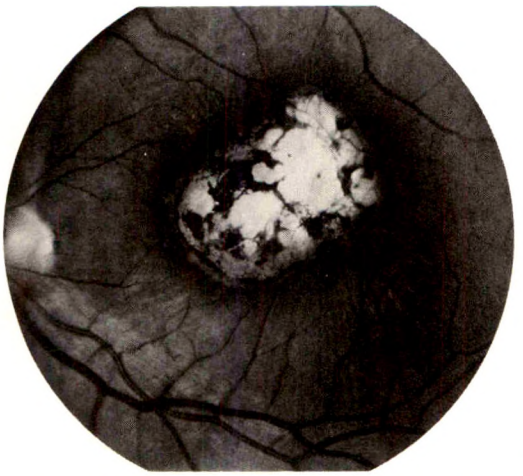

Fig. 11 (Ghartey and Brockhurst). Case 5. Fundus photograph taken two years after treatment shows a healed flat retinochoroidal scar.

Discussion

Retinochoroiditis presumably caused by toxoplasmosis is difficult to diagnose. Serologic tests are helpful, but, as noted by Feldman,[8] many may not be found increased to significant levels even during an active ocular *Toxoplasma* infection. Most laboratories consider serologic titers of less than 1:64 as negative. However, Jacobs, Fair, and Bickerton[9] showed that active *Toxoplasma* disease may be present in an eye with a titer of less than 1:64. In our Case 4 initial repeated serologic tests were negative, less than 1:64 for *Toxoplasma* antibodies. We, therefore, consider a morphologically compatible lesion, a titer of 1:2 or more, and the absence of any other cause of the lesion as the most important criteria for diagnosis.

According to Beverly,[2] the initial *Toxoplasma* infection is caused by a live organism. Recurrent toxoplasmic retinochoroiditis is generally believed to be the result of the following: (1) re-activation of infection with gross local proliferation of free forms after rupture of a cyst; or (2) hypersensitivity reaction of the delayed tuberculin type, either to *Toxoplasma* cyst contents or tissue breakdown products.

Photocoagulation destroys the organism if its location can be identified and probably denatures the antigenic proteins in the hypersensitivity reaction. The one patient who failed to respond to photocoagulation had marked lens and vitreous opacities. We believe that these opacities prevented adequate treatment of the lesion even with the red III power of the xenon arc photocoagulator.

The purpose of photocoagulation treatment is to decrease morbidity, shorten the prolonged period of disability, and possibly prevent recurrences in refractory cases. The duration of systemic treatment in our patients varied from two months to 2½ years, with an average of 11 months. The four patients whose lesions healed within two months after photocoagulation all had relatively clear media and localized retinochoroiditis. These patients have not developed any recurrences during the period of follow-up, which varies from six months to seven years.

Because of the favorable results observed, we believe that photocoagulation should be used in localized toxoplasmic retinochoroiditis which proves to be refractory to medical treatment in those patients who cannot tolerate medical therapy. Photocoagulation has its own complications and requires careful selection of cases. In our series, two eyes (Cases 3 and 5) developed preretinal folds after treatment with photocoagulation. Fortunately, the folds were not severe enough to affect the final vision in these cases. We believe the most suitable lesions are those that have partially healed, leaving a central, gray, active nidus, which proves to be refractory to

prolonged systemic medication and that is threatening macular vision, or in cases in which the patient develops severe complications to the systemic medications.

Summary

Active, recurrent, protracted toxoplasmic retinochoroiditis that had been unresponsive to intensive medical therapy with pyrimethamine, sulfamethoxypyridazine, intramuscular folicic acid, or clindamycin and corticosteroids, was treated with photocoagulation in five eyes.

Four eyes healed rapidly within a few weeks. In one patient's eye, lens and vitreous opacities prevented adequate treatment with the red III intensity level of the xenon arc photocoagulator. Subsequent surgical diathermy and cryocoagulation resulted in prompt healing of the lesion.

Noninvasive photocoagulation of active toxoplasmosis retinochoroiditis is recommended in protracted cases if the media are clear, the macula is threatened, or there are severe complications from systemic medications.

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CENTRAL ANTERIOR CHAMBER DEPTH AFTER LASER IRIDECTOMY

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Many ophthalmologists believe that the anterior chamber deepens as a result of successful peripheral iridectomy in angle-closure glaucoma. This belief may be partly the result of a statement to this effect made by Barkan,[1] but more importantly the result of slit-lamp examinations after iridectomies in which the appearance on casual inspection seems highly supportive of the impression of anterior chamber deepening. Central deepening may occur from zonular tightening after the use of cycloplegics postoperatively, a phenomenon not related per se to the breaking of the pupillary block.[2] That central deepening occurs in the absence of postoperative cycloplegics has been refuted by several authors.[3-6]

Previous observations of central postoperative chamber depth have been made after surgical iridectomies. To the best of our knowledge, no reports have been no published concerning central chamber measurements after laser iridectomy that exclude possible influence of surgical alteration of global integrity. We performed such measurements after outpatient argon laser iridectomies.

MATERIAL AND METHODS

Ten eyes in seven patients, all with the diagnosis of chronic angle-closure glaucoma, underwent successful argon laser outpatient iridectomy. In each case, successful perforation of the iris was achieved in a single session. Preoperative preparation consisted of a miotic series of 4% pilocarpine and 650 mg of aspirin administered orally one hour preoperatively. Four irides were gray and six were brown. Two of the latter, in black patients, were heavily pigmented. Perforations were achieved with multiple burns using a 50-μ spot size, 0.1 second duration, with peak energy levels varying from 400 to 1,500 mW, as required by the individual iris. Postoperative management consisted of topically administered corticosteroids at two-hour intervals for one day and 650 mg of aspirin at six-hour intervals for the same period. In each case, one drop of 1% tropicamide was applied at the termination of the procedure.

Measurement of the anterior chamber depth, in conjunction with slit-lamp examination and gonioscopy, was made using the variable slit-height method previously described.[7] These measurements were made after the preoperative miotic series had achieved its maximum effect and were repeated at such various intervals postoperatively (Table) that any deepening effect attributable to cycloplegics was absent.

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TABLE

CENTRAL ANTERIOR CHAMBER DEPTH AFTER LASER IRIDECTOMY

Patient No.	Sex	Age (yrs)	Race	Eye	Anterior Chamber Depth: Preoperative	Anterior Chamber Depth: Without Postoperative Miotics	Anterior Chamber Depth: With Postoperative Miotics	Postoperative Interval
1	F	47	W	R.E.	1.80	1.90	1.90	5 mos
2	F	79	W	R.E.	1.65	1.65	—	6 mos
				L.E.	1.65	1.65	—	6 mos
3	F	65	W	R.E.	1.50	1.50	—	1 mo
4	F	74	W	R.E.	1.50	1.50	—	2 mos
				L.E.	1.50	1.50	—	2 mos
5	F	49	B	L.E.	1.65	1.65	—	1 wk
6	M	79	B	R.E.	1.50	1.50	—	1 mo
7	F	53	W	R.E.	1.65	1.80	1.65	2 wks
				L.E.	1.65	1.80	1.65	1 wk
		Mean average			1.60± 0.10	1.65± 0.14		

RESULTS

As seen in the Table, the average preoperative central chamber depth with miotics was 1.60 mm and the corresponding average postoperative measurement without miotics was 1.65 mm. Examinations were made at various intervals postoperatively, but at a sufficient period after laser iridectomy so that any possible associated inflammatory sequellae or cycloplegic medication that could affect chamber depth was absent. Despite the small number of subject eyes, a two-tailed paired sample *t*-test for the difference between the preoperative and postoperative mean depth measurements failed to show a difference ($P > .05$), as anticipated from simple inspection of the findings. However, in all eyes a prominent deepening of the chamber angle occurred postoperatively except in those areas limited by peripheral anterior synechiae.

In all cases but three, the central depth was identical at both measurements. In these three exceptions, an increase in chamber depth of 0.10 to 0.15 mm, representing an increase of 6 to 10% of the original depth, was found after iridectomy. However, instillation of one drop of 4% pilocarpine shallowed the anterior chamber to the preoperative depth in two of these eyes.

DISCUSSION

Increase in the central anterior chamber depth postoperatively was not observed either clinically or statistically. The true deepening of the anterior chamber is confined to the periphery, although casual slit-lamp observation gives an impression of generalized deepening of the entire chamber. At the time of the measurements, there was no residual effect of the weak cycloplegic used immediately postoperatively. These observations are consistent with the presently accepted concept of angle closure caused by pupillary block.[8] Iridectomy relieves the pressure gradient between the posterior and anterior chambers, bypassing the relative pupillary block at the lens surface, thereby alleviating the iris-bombé. Iridectomy does not, however, cause a retromovement of the lens with a deepening of the central chamber.

As expected, variability in the placement of the iridectomy did not relate to the success of the procedure as long as it was peripheral to the collarette and not in an area of posterior synechiae formation. Similarly, the effect of the iridectomy was independent of the size of the perforation.

Barkan[1] stated:

> A deepening of the axial depth of the chamber, as measured by the Ulbrich drum was observed in many cases of chronic noncongestive narrow-angle glaucoma after iridectomy. It occurred within a short span of time (days or weeks) or over the course of several months.

In contrast, Tornquist,[3] Weekers and Grieten,[4] and Iuglio,[6] describe series of 16 eyes, 11 eyes, and ten eyes, respectively, in which there was no significant increase in the postoperative chamber depths. Lowe[5] did not measure the anterior chamber depth directly in his series but indicated agreement with the contention that the central anterior chamber depth does not increase after iridectomy.

In contrast to those seen after surgical iridectomy, central chamber depth changes after laser iridectomy are particularly significant, because the integrity of the globe has not been compromised. The various possible operative complications of surgical iridectomy that might affect the chamber depth, such as zonular rupture, vitreous loss, lens disruption, peripheral synechiae formation, disturbances in aqueous production, wound leaks, and gross alterations in the limbal anatomy, are absent in the laser procedure. Although some iritis and pigment dispersion are always seen after laser iridectomy, there is no reason to expect that these phenomena would affect the chamber depth significantly. In any case, they were not present at the time of the postoperative measurements in our series.

Our findings support the contention that the anterior chamber does not increase in depth after iridectomy. The widespread but unfounded impression that iridectomy deepens the chamber generally is probably consequent to a combination of peripheral deepening as a result of the iridectomy, true central deepening caused by the postoperative use of strong cycloplegics, and the absence of preoperative, miotic-induced shallowing.[9]

Summary

We found the true anterior chamber depth to be unaffected by successful laser iridectomy in ten eyes treated by this modality for chronic angle-closure glaucoma. The apparent general deepening seemed to be the result of peripheral chamber deepening combined with the common use of strong cycloplegic agents, reversing the shallowing effect of preoperative miotic medications.

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ACUTE ANGLE-CLOSURE GLAUCOMA SECONDARY TO AN ANEURYSM OF THE POSTERIOR COMMUNICATING ARTERY

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The most common inciting cause of acute angle-closure glaucoma is a mid-dilated pupil in a person who has inherited a narrow anterior chamber angle.[1] Probably the dilation of the pupil is physiologic in most cases. Rarely, however, interruption of the parasympathetic supply to the sphincter pupillae muscle may initiate the attack.

CASE REPORT

A 57-year-old woman without a previous history of significant disease developed pain behind and above her left eye two hours before she was admitted to the hospital. The onset of the pain was coincident with lifting, and was associated with a sudden feeling of faintness and nausea. The patient said there had been some discomfort about the left eye for two to three days. She had also noticed mild redness of the eye associated with a scant watery discharge for three weeks before the pain developed.

The results of a neurologic examination were normal, except for findings of the partial left third nerve paresis. The right anterior chamber angle was narrow and the left chamber angle was closed over 75% of its circumference. Otherwise abnormal findings were limited to the left eye. Visual acuity was 6/18 (20/60). The pupil was oval vertically, 7 mm in diameter, and fixed. There was 3 mm of blepharoptosis of the upper eyelid. Ocular motility was full. The patient denied diplopia. The applanation intraocular pressure (IOP) was L.E.: 35 mm Hg and R.E.: 16 mm Hg. The conjunctiva was slightly red and edematous but the cornea and anterior chamber were clear.

Within two hours several applications of 2% pilocarpine had constricted the left pupil to 2 mm (3 mm in the right eye). The IOP in the left eye was 15 mm Hg. The pain was moderately reduced but pain and nausea persisted for several hours into the evening. She took meperidine HCl (Demerol) to relieve the pain. The next morning the pain was essentially unchanged but the left third nerve was totally paretic. The angle of the affected side was narrow but open throughout. The cerebrospinal fluid was grossly bloody and angiography showed a posterior communicating aneurysm. The neck of the aneurysm was ligated. A peripheral iridectomy was done on each eye a few weeks later.

Three months after the operation on the aneurysm the left upper eyelid began to lift slowly. Three months later best corrected visual acuity was R.E.: 6/6 (20/20) and L.E.: 6/7.5 (20/25). Color vision and fields were normal. A central scotoma could not be shown on the left., The right pupil was normal; the left pupil was 6 mm and oval. It was fixed to light and near stimuli but did react minimally on upgaze. The left upper eyelid had 1 to 2 mm of blepharoptosis and was elevated 1 to 2 mm on downgaze or adduction. The left eye was slightly hypotropic and exotropic. Adduction was 50% of normal on the left but abduction was normal. Upward and downward movements of the left eye were minimal. Horizontal optokinetic stimulation produced a normal response. Vertical optokinetic stimulation also produced horizontal movement of the left eye. Intraocular pressure was 15 mm Hg in each eye and the fundi were normal.

DISCUSSION

The clinical appearance in this patient suggested an acute attack of angle-closure glaucoma. However, several features indicate that it was not the usual case of acute angle-closure glaucoma. Even though the IOP was increased (35 mm Hg), a pressure of 50 mm Hg or greater would be more typical for acute-angle closure glaucoma. The closure of the anterior chamber angle over only 75% of its circumference probably accounts for the observed pressure level. The ease with which the pupil was constricted with 2% pilocarpine was unusual for acute angle-closure glaucoma. Even more significant, the pain was only minimally relieved by the miosis and pressure decrease. Other unusual features were the absence of corneal edema

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and photophobia and the mild redness of the eye for three weeks before the pain.

Angle closure secondary to pupil dilation was the mechanism that produced the increased IOP. Both eyes had narrow angles. The angle (involved side) was 75% closed on admission and the pressure decreased to 15 mm Hg with miosis and a resolution of the partially closed angle.

It is doubtful that a change in parasympathetic innervation affected the IOP in our patient. Experimental evidence indicates that in the presence of an open angle, interruption of third nerve parasympathetic fibers intracranially (the site of involvement in our patient) produces little, if any affect, on IOP in dogs. The procedure tended to decrease IOP,[2] which is consistent with the finding that an experimental destructive lesion in the area of the ciliary ganglion reduces IOP.[3] Probably both lesions decrease the flow of aqueous into the eye.

It is unlikely that our patient had an increased parasympathetic stimulation secondary to the aneurysm because the pupil was dilated. In any case, experimental stimulation seems to produce an increased outflow as well as an increased inflow.[4-6] The net effect is an IOP that is unchanged or reduced.

That a change in sympathetic innervation caused the increase in IOP is unlikely. It is difficult to see how there would be an interruption of the sympathetic supply to the orbit, because most sympathetic fibers enter the orbit with nerves other than cranial nerve III.[7] The skin of the face on the left did not show any difference in moisture, temperature, or color when compared with the other side and the pupil was dilated. Experimental interruption of sympathetic innervation in animals does not seem to produce any change in inflow, but may produce an increased outflow.[8-11] Stimulation of the preganglionic cervical sympathetic nerve produces a decrease in inflow and an increase in outflow.[8,12]

If there was an increased amount of epinepherine circulating because of the physiologic crisis, a decreased inflow and an increased outflow would be expected, which would produce a decreased IOP.[13,14] Extraocular muscle tension was probably not a factor because relaxation of the tension of the extraocular muscles would produce a decrease in IOP if any measurable change took place.[15]

Our patient had the unusual coincidence of a narrow angle in the presence of the third cranial nerve paresis. A similar situation might be expected in any individual with marked narrowing of the anterior chamber angle superimposed on a dilated pupil, as described by Zaidi.[16] His case involved third nerve paresis related to diabetes mellitus. As in our case, IOP was moderately increased and the attack of angle closure was easily broken with pilocarpine therapy. Similarly, no photophobia or corneal edema occurred. However, pain and redness of the conjunctiva did not occur in his patient. Whether the redness of the conjunctiva and the pain were related to a change in the sympathetic system, as may occur in cluster headache, is not certain.

In our case there was a marked, relative early involvement of the pupil in relation to the well-preserved ocular motility. Only rarely is such a transition of progressive oculomotor nerve palsy reported in the presence of a posterior communicating aneurysm.[17]

Summary

A 57-year-old woman developed pain behind and above her left eye. She had a partial oculomotor nerve paresis manifest by slight blepharoptosis and a dilated pupil. Both anterior chamber angles

were narrow but the left was partially occluded. There was no photophobia or corneal edema. Though the moderately increased intraocular pressure was controlled by medication, pain persisted and the oculomotor nerve palsy became complete 12 hours later. Cerebral angiography was done. She had an aneurysm of the left posterior communicating artery. The aneurysm was treated by neurosurgical techniques and the oculomotor paralysis resolved within a few months except for misdirection in regeneration.

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CENTENARY MEETING OF THE OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

The 1980 meeting of the Ophthalmological Society of the United Kingdom, under the aegis of Professor Norman Ashton, marked the 100th anniversary of the founding of the Society by William Bowman in 1880. The meeting was a magnificent ceremony of color and pageantry (Figs. 1 and 2), which provided an unforgettable experience for all who had the privilege of attending.

All British ophthalmology rallied to make the meeting a great success. President Ashton was assisted by the vice-presidents, P. L. Blaxter, J. E. Cairns, D. P. Greaves, and Redmond Smith; Editor, P. D. Trevor-Roper; Treasurer, F. W. Law; Assistant Treasurer, A. D. McG. Steele; and the Honorary Secretaries, J. S. Shilling and A. H. Chignell.

Fig. 1 (Newell). The Armorial Bearings of the Society, granted in 1965. "Sable on an open Book proper edged and bound an Eagle rising Or on a Chief wavy Gold a representation of the Eye of Horus of the Field And for the Crest On a Wreath Or and Vert In front of a demi Archer habited Vert sleeved and belted Gules hooded Sable Bow in full draught to the dexter proper four Escallops Or as the same are in the margin hereof more plainly depicted. . . .On the dexter side a figure representing Apollo proper holding in the exterior hand a Lyre Or and on the sinister side a representation of a Franciscan Friar holding in the exterior hand a Magnifying Glass." The Bearings are of course in livery colors.

The meeting opened with a Thanksgiving Service in Westminster Abbey. The music was provided by the Royal Army Medical Corps and fanfares were played by trumpeters from the Royal Military School of Music.

Representatives in clerical, military, and academic uniform participated from all over the world. The procession was led by representatives of the medical services of the British Armed Forces followed by representatives of the British Red Cross Society, The Worshipful Company of Barber-Surgeons, The Worshipful Company of Spectacle Makers, The Worshipful Society of Apothecaries of London, representatives of the University of London, colleges and medical societies, including The Royal College of Physicians of London, The Royal College of Surgeons of England, The Royal College of Physicians of Edinburgh, The Royal College of Surgeons of Edinburgh, The Royal College of Obstetricians and Gynaecologists, The Royal College of General Practitioners, The Royal College of Pathologists, The Royal Society of Medicine, The Royal College of Nursing of the United Kingdom, The British Postgraduate Medical Federation, The British Medical Association, The Faculty of Ophthalmologists, The Association of Clinical Pathologists, and the ophthalmic section of the Royal Society of Medicine. These were followed by representatives of the orthoptists, opticians, ophthalmic nurses, eye hospitals of the United Kingdom, the European Ophthalmological Society, the Academia Ophthalmologica Internationalis, the International Coun-

cil of Ophthalmology, and fifteen ophthalmic societies affilitated with the Ophthalmological Society of the United Kingdom Members of The Most Venerable Order of St. John of Jerusalem were in full Crusader attire. They were followed by the members of the Council of the Ophthalmological Society of the United Kingdom and the chaplains of Moorfields Eye Hospital and representatives of churches.

The Abbey was filled with these groups as well as representatives of blind groups, nursing groups, and visitors. The Lord Mayor of Westminster was received and conducted to his seat in the choir, followed by His Royal Highness The Duke of Gloucester, Grand Prior of the Knights of St. John. His Royal Highness, The Prince Philip, Duke of Edinburgh was received in the church with a fanfare. The Dean of Westminster opened the Thanksgiving. The hymns selected referred particularly to light, vision, and the eyes. The lessons were read by Mrs. M. D. Carmichael, Life President of the International Ophthalmic Nurses Association, and by Professor Norman Ashton. The Westminster Choir sang the CXXI Psalm, "I will lift up mine eyes unto the hills: from whence cometh my help. . . ." The Lord Bishop of Salisbury delivered the sermon and the services closed with the British national anthem, "God save the Queen," which was played with a fanfare of trumpets. The services were followed by luncheon in the Great Hall of Westminster School.

The opening scientific program was a symposium devoted to "Then and Now," contrasting ophthalmic knowledge in 1880 with 1980. President Ashton described William Bowman's skill as an artist, and he described the history of the lithography of Bowman's plates for his publication concerning voluntary muscle in the proceedings of the Royal Society.

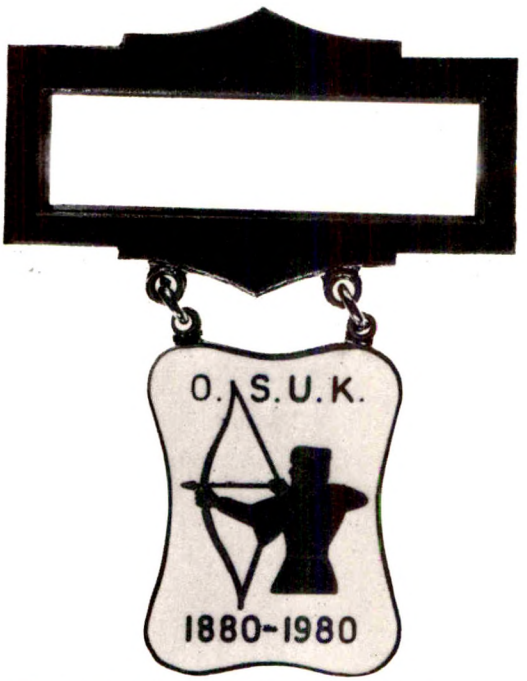

Fig. 2 (Newell). The crest of the Arms was used in the design of the lapel badge provided for those attending the Centenary Meeting.

President Ashton had even found the original drawings from which the lithographs were made. Professor A. Edward Maumenee discussed uveitis; Sir Stephen Miller, glaucoma; Professor Paul Henkind, the retina; Professor Barrie Jones, trachoma; and Patrick D. Trevor-Roper provided a most engaging vignette on therapy.

Lorenz Zimmerman gave the 48th Bowman Lecture. His topic was uveal melanomas. His major plea was for careful observation of small tumors rather than immediate enucleation. He emphasized that there has been little change in the prognosis of melanomas of the uvea throughout the years.

The following morning J. R. Hudson chaired a symposium on retinal detachment. In the afternoon, P. L. Blaxter chaired a symposium on medical ophthalmology. President Ashton presided at the session on ocular pathology the

following morning, and in the afternoon Redmond Smith chaired a symposium on cataract surgery.

The annual dinner was an exciting event. More than 500 guests had gathered from more than 60 countries. The dinner was followed by the traditional toasts to the Queen, to the Society, and to the guests with the appropriate responses.

One of the features of the meeting was "A Hundred Years of History of the Ophthalmological Society of the United Kingdom," written by Frank W. Law. Mr. Law has been Honorary Treasurer of the Society for 33 years. Earlier he had published a sequel to Treacher Collins's first volume of the history of Moorfields Eye Hospital.

The officers of the Ophthalmological Society of the United Kingdom had presented a presidential badge to the Ophthalmological Society of Australia in 1969. This year, the Ophthalmological Society of Australia reciprocated with a silver chain for the presidential badge of the Ophthalmological Society of the United Kingdom.

The meeting was outstanding in every respect. It reflected the careful planning of President Ashton and the Council, which included, in addition to the officers named above, the following: R. K. Blach, A. G. Cross, R. B. Harcourt, R. J. Marsh, M. J. Roper-Hall, D. F. Woodhouse, C. A. Brown, S. J. Crews, T. J. ffytche, G. I. Scott, J. E. Wright, and M. H. Whiting.

FRANK W. NEWELL

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PITUITARY TUMORS REASSESSED

In light of recent electron microscopic and immunohistochemical studies, the time-honored classification of pituitary tumors on the basis of light microscopic staining characteristics is no longer valid.[1-5] Agranular tumors at a light microscopic level (chromophobe) almost invariably contain secretory granules identifiable by more refined techinques.[3] Tumors devoid of visible granules can produce acromegaly,[6-7] Cushing's disease,[8-9] and Forbes-Albright syndrome.[5,10-15]

The lobules of the normal pituitary gland are composed of six cell types.[3,4] Five of these are responsible for secretion of the hypophyseal hormones under the control of the hypothalamus (Table 1). This sixth cell is called a follicular cell, and it has no known secretory function. Recently, specific radioimmune assays have been developed for each of the hypophyseal hormones. Any of these cells may proliferate and produce a secreting adenoma which may or may not be accompanied by clinical minifestations.[5,8] Tumors unaccompanied by clinical manifestations are classifed as nonsecreting, and those tumors associated with syndromes related to hypersecretion of hormones are termed secreting tumors (Table 2.)

It is possible that a major unforeseen problem will be created by the development of specific radioimmune assays for each of the hypophyseal hormones, especially prolactin, and by the identification of a specific pathoetiology for many clinical syndromes previously classified as idiopathic in nature. A bold but appropriate neurosurgical intervention using microsurgical transsphenoidal techniques on microadenomas[5,9,12,13,15] of the pituitary gland is often indicated. Some estimate of the magnitude of this problem in terms of appropriate surgical intervention may be obtained from recent published reports. McCormick and Halmi[16] have demonstrated asymptomatic pituitary adenomas in 9% of 1,600 consecutive autopsies. Perhaps as many as 80% of these tumors are potentially prolactin-secreting.[10,17] Additionally, 15 to 20% of nonpregnant amenorrheic women and 11% of infertile oligospermic

TABLE 1

ANTERIOR PITUITARY HORMONES AND HYPOTHALMIC REGULATORS*

Cell Type	Hormone	Hypothalmic Regulator
Somotrophic	Growth	GH-releasing and GH-inhibiting factors
Lactotrophic	Prolactin	Prolactin-releasing and prolactin-inhibiting factors
Gonadotrophic	Follicle-stimulating	Gonadotrophin-releasing factor
	Luteinizing	Gonadotrophin-releasing factor
Corticotrophic	ACTH	ACTH-releasing factor
Thyrotrophic	Thyroid-stimulating	TSH-releasing factor

*Adapted from Abboud and Laws.[18]

men may have hyperprolactinemia.[12] Abboud and Laws[18] categorically stated that, "Hyperprolactinemia is the hallmark of endocrine abnormality."

Prolactinemias can be divided into those contained within the sella turcica, microadenomas, and those of large size (macroadenomas) (Table 3).[5,9-13,15,19,20] The ergot-derivative (2-bromo-α-ergocryptine)[7,11,15,17,21-27] is a dopamine agonist that effectively regulates prolactin levels in almost all patients with prolactin-secreting adenomas. It also reduces tumor size significantly in patients with macroadenomas.[24,26,27] Apparently the most effective therapy for prolactin-secreting microadenomas is transsphenoidal surgery, but bromocriptine therapy should be recommended in patients with macroadenomas.

Recently, Tyrrell and associates[9] have demonstrated the efficacy of selective resection of pituitary microadenomas by the transsphenoidal approach in patients with Cushing's disease. In their series of 22 patients, routine plain skull radiography did not reveal generalized enlargement of the sella turcica in any patient. Biplane hypocycloidal polytomographic results were abnormal in 14, but eight patients had normal radiographic studies. They believe most patients with Cushing's disease have secreting tumors of the pituitary gland and that microadenomectomy is the preferred treatment. We can infer from their paper that Nelson's syndrome associated with an

TABLE 2

CLASSIFICATION OF PITUITARY ADENOMAS

Hormone Secreted	Associated Clinical Manifestation
ACTH	Cushing's disease; Nelson's syndrome
Growth	In children, gigantism; in adults, acromegaly
Prolactin*	In women amenorrhea-galactorrhea, Forbes-Albright syndrome, Chiari-Frommell syndrome; in men, decreased libido, oligospermia
Thyroid-stimulating	Thyrotoxicosis (rare)
Follicle-stimulating	Precocious puberty
Luteinizing	Precocious puberty
None	Isolated or combined hypopituiarism

*Nonsecreting tumors may also produce prolactin.

TABLE 3

PROLACTINOMAS

Microadenomas	Macroadenomas
Greater incidence in females	Greater incidence in males
Prolactin median, 500 ng/ml	Prolactin median, 800 ng/ml
Transsphenoidal surgery will cure 80%	Transsphenoidal surgery will not return prolactin levels to normal
	Tend to be aggressive
	41% cause visual impairment
	Postsurgical prolactin median, 200 ng/ml

aggressive pituitary macroadenoma is an iatrogenic disease, that is, early transsphenoidal surgery for an ACTH-secreting pituitary tumor will prevent the development of this syndrome complex.

The availability of specific radioimmune assays for pituitary hormones, the refinement and identification of hypothalamic controlling substances, the discovery or development of new blocking agents, and the continued decrease in the morbidity of transsphenoidal microsurgery may make the chiasmal syndrome, as we fondly know it, noteworthy for its rarity.

R. M. BURDE

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CORRESPONDENCE

Letters to the Editor must be typed double-spaced on 8½ × 11-inch bond paper, with 1½-inch margins on all four sides, and limited in length to two manuscript pages.

Food and Drug Administration Implant Follow-up

Editor:

The matter of implant patients who are ultimately lost to follow-up by the Food and Drug Administration (FDA) is of great concern to all of us. It is possible for patients with complications or those requiring lens removal to be treated by physicians who are not implant investigators and who are under no obligation to report their activities. Many investigators may also feel they have no obligation to report difficulties they see in patients .

To reduce even farther the already low loss to follow-up rate and to enhance the validity of the FDA study, the American Intra-ocular Implant Society strongly recommends that all ophthalmologists, whether investigators or not, consider the following recommendations:

1. If your implant patients leave the area, make sure their continued follow-up is reported either by you or by their new ophthalmologist (follow-up by telephone if necessary).
2. An ophthalmologist (investigator or not) who receives a patient postoperatively should make contact with the implant surgeon and arrange for continuous reporting on the patient.
3. In the rare event a patient does not recall who the implanting surgeon was and if the implant was done after Feb. 9, 1977, you may obtain this information by telephoning the Intraocular Lens Manfacturers Association at 213-596-9397.
4. Ophthalmologists who are not investigators should take on the responsibility of investigators if they accept an implant patient to follow-up.
5. Investigators should advise their noninvestigator colleagues of the importance of this for an accurate study.

We hope all ophthalmologists will continue to cooperate in a professional manner as we have in the past to insure that this FDA study of intraocular lenses is the best possible.

KENNETH J. HOFFER, M.D.
American Intra-Ocular Implant Society
Santa Monica, California

Filter Failure

Editor:

Recently our Coherent Radiation laser, the argon model 800, which was purchased in 1972, had an extraordinary breakdown. While one of us was using the laser, it became obvious that scattered argon light was entering the left eye of the surgeon. On examining the laser, we found that there was no filter in front of the left eye during the delivery of the light to the patient. The right eye had the filter in place.

There are two filters, disk shaped in nature, that are rotated into place during photocoagulation, covering the right and left eye independently. The filter in the left eye became loose and fell out because of the failure of the epoxy cement. Therefore, argon light entered the surgeon's eye.

We think this may be a significant complication after several years of use and that those who are using Coherent Radiation photocoagulators should be aware of this potential danger. This problem can be detected only by closing one eye at a time, and testing each filter

separately. There is no fail-safe mechanism to prevent the machine from firing in spite of filter failure.

J. B. WALSH, M.D.
B. E. WRIGHT, M.D.
Bronx, New York

Reply

Editor:

Only a few of the early Model 800 photocoagulators were produced with the safety filters dependent upon epoxy cement. We soon discovered that the frequent opening and closing of the filter assembly tended to jar loose the filter lenses and, consequently, we added screws to eliminate this failure.

The Model 800 was superceded by the Model 900 in 1975 but filter conversion kits are still available for the 800 on special order. We have recommended for several years that any customers who have the early units consider replacement or conversion and we do offer a trade-in allowance for the old unit. A routine inspection of this aspect of the early Model 800 units is advisable.

R. J. BURKE, PH.D
Coherent Radiation,
Palo Alto, California

Occupational Exposure and Choroidal Melanoma

Editor:

We recently read with interest the article, "Increased incidence of choroidal melanoma occurring in a single population of chemical workers," by D. Albert and associates. (Am. J. Ophthalmol. 89:323, 1980). They found a statistically significant increase in choroidal melanomas among present or former workers of a chemical plant, making a strong case for occupational exposure as an etiologic factor.

This paper brought to mind an earlier work by Rahi,[1] in which complement-dependent cytotoxic antibodies were identified in some patients with choroidal melanomas. These antibodies were patient-specific and there was no cross-reactivity between serum from one patient and tumor from another patient. This suggests that there are new antigens on the melanoma cell surface which are patient-specific and probably comparable to the tumor-specific transplantation antigens (TSTAs) that have been observed in other types of malignancy. This is not to be confused with the intracellular antigen found in all melanomas. Antibodies to this antigen are not patient-specific and can be found in almost all patients with choroidal melanomas.[2,3] One of the interesting applications of this work on other tumors has been the finding that chemically induced tumors possess unique TSTAs, while virus-induced tumors typically share TSTAs with other tumors caused by the virus.[4,5] Since Rahi's work[1] suggests that choroidal melanomas have unique TSTAs, this is consistent with a chemically induced tumor, which is of particular note in light of the work of Albert and associates. If this association holds, one would certainly expect to find a number of papers in the near future relating environmental exposure and choroidal melanoma.

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Optic Nerve Hypoplasia and Young Maternal Age

Editor:

In their article "Optic nerve hypoplasia associated with absent septum pellucidum and hypopituitarism" (Am. J. Ophthalmol. 89:113, 1980), W. Krause-Brucker and D. W. Gardner have thoroughly documented the neuro-ophthalmic and neuro-endocrine dimensions of optic nerve hypoplasia in five children. The authors noted that all the children were first-born, but they reported maternal age at delivery only in Case 1 (21 years).

One feature not brought out in their article is important. Two recent reports point out that children with optic nerve hypoplasia often have extremely young mothers.[1,2] In a small sample, 14 mothers of such children had a mean age of 20.0 years at delivery, whereas the mean age of all mothers at delivery in that state during a recent year was 24.7 years.[2]

We have recently encountered two patients with severe bilateral optic nerve hypoplasia (both had normal computed axial tomograms and were not clinically hypopituitary). The mothers, in each instance 16 years old and unmarried, adamantly denied drug use during pregnancy.

Further epidemiologic study of patients with optic nerve hypoplasia is needed. Maternal and paternal age, history of drug exposure during pregnancy, gravidity, and marital state should be studied as well as central nervous system structure and pituitary-hypothalamic function. The disorder may be intrinsic to pregnancies of very young women, as monosomy X appears to be,[3] or it may be caused by experiences more common among young women, among which must be the use of therapeutic or recreational drugs.

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Malignant Glaucoma and Fluid Flow Rate

Editor:

I wish to add a comment to the excellent study "Experimental perfusions through the anterior and vitreous chambers with possible relationships to malignant glaucoma" by D. L. Epstein, J. M. Hashimoto, P. J. Anderson, and W. M. Grant (Am. J. Ophthalmol. 88:1078, 1979). These authors concluded that increased pressure in the space behind a posteriorly detached vitreous leads to a decrease in fluid movement through the vitreous gel. Experimental studies with bovine and rabbit vitreous have been performed which provide a confirmation of these data. Fatt[1] measured the hydraulic flow conductivity of animal vitreous in vitro, noting that with increased pressure on the gel it became dehydrated and the fluid conductivity decreased. A 60 to 70% decrease in water content led to a decrease in conductivity of about one half. This phenomenon is observed in all connective tissues, with the vitreous acting in this circumstance like a highly hydrated connective tissue.

One potential explanation for the occurrence of malignant glaucoma, then, is the following: (1) an initiating event

occurs to increase the posterior force applied to the vitreous gel (for example, increased fluid pressure in the cavity posterior to the detached vitreous); (2) fluid flows through the vitreous toward the anterior chamber at an increased rate, but some compaction (in effect, dehydration) of the gel occurs; (3) due to the compression, the fluid conductivity of the vitreous gel decreases, and with continued higher pressure from posteriorly, the gel undergoes further decrease in conductivity, setting up a vicious circle; (4) the compressed vitreous gel is moved forward physically by the posterior-to-anterior pressure difference, apposing some portions of the gel to anterior structures (ciliary body, lens, iris), and thereby decreasing the available surface area for water leaving the anterior surface of the gel. This would lead to an intensification of the decrease in fluid permeability of the vitreous as well as to shallowing of the anterior chamber.

This proposed sequence, which is simply restated in modified form from Epstein and associates, incorporates the data of Fatt, and seemingly provides a reasonable explanation for the clinical features of malignant glaucoma as well as its therapy. Osmotic agents would, by decreasing the fluid contents of the vitreous cavity, lower the pressure behind the vitreous, allowing improved fluid conductivity and sometimes restoring normal tissue relationships and intraocular pressure. Surgical disruption of the vitreous gel structure (either centrally via the pupil, or through a pars plana approach) would prevent the reoccurrence of the cycle since there would be no intact vitreous gel to act as a diaphragm across the entire globe.

In unpublished experiments carried out with Jonathan Pederson, I have demonstrated a similar phenomenon in aphakic eye bank eyes. In six such eyes, when the fluid pressure behind the vitreous body was increased only modestly, the vitreous body and iris moved forward to flatten the anterior chamber. This occurred when the pressure in the posterior vitreous cavity (behind the detached vitreous body) was raised a few millimeters of mercury above the anterior chamber pressure. In one eye in which the vitreous gel was disrupted prior to experimental manipulation (presumably at the time of cataract extraction), fluid flowed easily into the anterior chamber and the resistance to fluid movement was apparently negligible.

We are still left, however, with explaining how the initial increased pressure behind the vitreous body occurs. When the process occurs at the time of surgery, the anterior chamber pressure is reduced to atmospheric pressure as it is opened. Thus, there is surely a higher pressure behind the vitreous, providing the initiating event. Yet, in some eyes, malignant glaucoma occurs long after surgery or even in an unoperated eye.[2] In these cases, if the fluid causing the pressure difference comes from the ciliary body, how does it move through or behind the vitreous without being able to return forward just as easily? Could the increase in pressure come from abnormal fluid dynamics in the posterior pole—for example, increased transudation or decreased reabsorption of fluid in the retinal or choroidal circulation? Or is the vitreous the primary element, with some patients developing poor fluid conductivity so that the most minimal pressure difference from posterior to anterior sets off the malignant cycle?

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Oxygen Permeability of Contact Lenses

Editor:

In the article, "The microbial flora in extended-wear contact-lens wearers" (Am. J. Ophthalmol. 88:543, 1979), by G. Smolin, M. Okumoto, and R. A. Nozik, the oxygen permeability of a contact lens was expressed as a percentage. I realize that this manner of expressing the oxygen permeability of contact lenses is often encountered in published reports. However, this terminology is incorrect and should not be used. The oxygen permeability of a contact lens must be expressed by a permeability coefficient ($P = D \cdot k$) in units that represent the amount of oxygen transported through a lens of unit area in unit time by unit driving force. The custom of using "oxygen percent" to characterize the permeability of contact lenses originated from the work of Hill, Fatt, and others.[1] The technique detects a "short-term oxygen debt" on the cornea by a given lens, and is expressed as the "equivalent oxygen percent" that would produce the same effect on the cornea.

Undoubtedly, this oxygen percentage is related to the oxygen permeability coefficient of the contact lens, or, even better, to the oxygen transmissibility of the lens ($D \cdot k/L$, where L is the thickness of the lens). Incidentally, in my opinion, the short-term oxygen debt produced on the cornea by a lens provides a useful indication of contact lens performance. But this is not the point. When an author wishes to give the oxygen permeability coefficient for a given lens, he should use the proper units. If he wishes to give the short-term equivalent oxygen debt, it should be so designated.

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BOOK REVIEWS

Advances in Ophthalmology: Volume 40. Edited by M. J. Roper, H. Sautter, and E. B. Streiff. Basel, Switzerland, S. Karger AG, 1980. Hardcover, 224 pages, introduction, 55 black and white figures. $106.60

The 40th volume of Advances in Ophthalmology contains three monographs. Two of the three will be of great interest to the readers of this journal and one probably of interest only to research workers.

The most important is probably the initial article on demography and causes of blindness throughout the world by Dr. Goldstein of Bethesda, Maryland. In the introduction, the author explains the difficulty of gathering reliable data. The definition of blindness varies enormously around the world and the personnel needed to determine the causes of blindness are frequently unavailable in the less developed parts of the world. The best data are probably collected in the United States through a mechanism set up by the author some years ago. He established a model reporting area consisting at first of a few states and more recently of between 14 and 16 states. Further, a strict definition of blindness was established so that reporting might be comparable from state to state. These surveys now include about 30% of the population of the United States. Of great interest to ophthalmologists are two factors: first, that of the population over the age of 65, 0.75% are blind; second, that the most common cause of blindness is "other retinal disease," mainly senile macular degeneration. The author makes a plea for a uniform definition of blindness and better collection of data with reference to incidence rather than just prevalence.

The second article is on protein in the aqueous humour and this will be of

interest primarily to investigators in the field of ocular physiology and biochemistry.

The third article, entitled "First Interprofessional Standard for Visual Field Testing," is the report of a working group on visual fields. Although the findings do not have immediate applicability to the practice of ophthalmology, some very important evaluations are made of visual field testing and of the future of automated perimetric systems. The authors feel that the most important step to be taken at this time is standardization of target contrast, angular size, background luminance, exposure duration, patient reaction time, and fixation. The effect of these variables is not as yet known and until these data are available establishment of an absolute standard for visual field testing is difficult. The directions for the future are clearly marked out by this article.

DAVID SHOCH

Retinal Detachment Surgery. By A. H. Chignell. Berlin, Springer-Verlag, 1980. Hardcover, 166 pages, index, 50 black and white figures, one color plate. $35.80

This book is divided into five main sections. The first deals with production, including pathogenesis, progression, predisposing factors, characteristics of rhegmatogenous retinal detachment, its symptoms, and methods of examination emphasizing ophthalmoscopy and visual fields. The second considers preoperative examinations including slit-lamp, indirect ophthalmoscopy, three-mirror lens, and findings of importance. The third covers preoperative management and planning of the operation, the fourth surgical details, and the fifth postoperative management and complications.

The book is generally well written and concise, with relatively few typesetting errors. The style is a summary form; and the illustrations range from adequate to artistic. The terms used may not all be immediately familiar to American ophthalmologists, for example, massive fibrosis of the retina and "U"-shaped tears, but the meanings are quickly evident. Some of the statements quoted by the author are from recent articles which perpetuate archaic thoughts. Also, some statements are too definitive—using the word "always" as opposed to "usually," or saying that traction is "inevitable" at a perforation site with retinal incarceration. The view that a giant tear is an extreme form of the horse shoe-shaped tear is not generally held. The prediction of the location of a retinal hole according to the distribution of the subretinal fluid cannot be regarded as invariably reliable. The disk, as shown in some drawings and as stated in the text, is not centrally placed but lies slightly to the nasal side of the fundus. Cobblestone degeneration is generally not regarded as drusen-like bodies with hyperpigmented borders but rather a chorioretinal atrophy usually interchangeably referred to as paving-stone degeneration; neither term is helpful.

A few inconsistencies appear. For example, while the prognosis for successful scleral buckling operations in patients with massive periretinal proliferation is poor, the injection of silicone oil is not preferred over combined scleral buckling and vitrectomy, as implied in the discussion of silicone oil usage; yet this statement is corrected in the discussion of detachments associated with intraocular fibrosis.

The surgical chapter is almost entirely limited to operations that require cryotherapy, silicone sponge explant, and encirclement but is well and tersely covered.

As in any book of this type, there are

bound to be minor faults and differences of individual interpretation. There is a good balance in the references, citing different viewpoints to stimulate thought and further investigation by the reader.

From his residency onward the library of every ophthalmologist should be augmented by a number of books on the various subspecialities in the field. This is a fine introductory book, particularly written for residents, given them a quick (166 pages), comprehensive, inexpensive, primer on the subject of retinal detachment.

PETER H. MORSE

Atlas of External Diseases of the Eye. Volume III. Cornea and Sclera. By David D. Donaldson. St. Louis, C. V. Mosby Company, 1980. Hardcover, 506 pages, preface, index, 408 illustrations, 112 stereoscopic views in full color on 16 View Master reels. $89.50

This is the second edition of volume III of this series. Dr. Donaldson's reputation as an ophthalmic photographer is well known to all ophthalmologists and, in my opinion, the steroscopic photographs obtained with the Donaldson External Camera are superb. Therefore, one would expect an atlas of Dr. Donaldson's stereoscopic photographs of the cornea and sclera to provide a treasure of photographic materials. Unfortunately, this is not the case.

The first criticism I have is that no place in the forward does Dr. Donaldson define for whom he is writing this text. Dr. David C. Cogan's forward is repeated from the 1971 first edition and states that it is intended for "students, practitioners and others concerned with ocular disease." If this is true, I feel that the selection of diseases illustrated by the stereoscopic photographs and the text portion of the Atlas is too limited and brief for students or residents in ophthalmology.

My second criticism is that the second edition contains few new stereoscopic color photographs. The only changes are in the areas of corneal dystrophies where an example of dot dystrophy takes the place of juvenile epithelial dystrophy, Reis-Bückler dystrophy is discarded for hereditary recurrent erosion, and fleck dystrophy is added. Additionally, a photograph of microcystic degeneration has been deleted. Although there is more text in this edition, including black-and-white illustrations (such as giant papillary hypertrophy secondary to contact lens wear), there are no color stereoscopic photographs to supplement these new additions. Another criticism is the poor quality of some of these stereoscopic photographs. For instance, the photograph of corneal clouding secondary to rubella syndrome is a poor illustration of corneal clouding. Important syndromes such as mucopolysaccharidosis are not illustrated in color stereoscopic photographs, whereas an extremely rare condition, urate keratopathy (which looks the same clinically as band keratopathy), is. There are good descriptions and photographs of fleck and central cloudy dystrophy of François. However, the more important dystrophies such as Fuchs dystrophy with cornea guttata and lattice dystrophy are poorly illustrated in the stereoscopic photographs. Additionally, the posterior crocodile Shagreen and central cloudy dystrophy of François look the same.

The stereoscopic photographs in the section on postoperative complications are outstanding, particularly with regard to epithelial downgrowth, postoperative infection, and anterior chamber cysts. In the section on herpes, it would have been helpful had there been a differentiation between the herpes zoster dendritic keratitis and the herpes simplex den-

dritic keratitis. There is not even a discussion in the differential diagnosis in the text. There are no photographs of important conditions such as limbal dermoid, cleft syndromes, pemphigus, or acne rosacea keratitis. There is no discussion of the similarities seen in chloroquine and Fabray's keratopathies.

On the whole, this atlas is disappointing. The selection of photographs and their quality are far from what I would have expected from Dr. Donaldson's collection. This text is for the specialist in external corneal disease who may find value in the rare dystrophies that are illustrated.

DONALD J. DOUGHMAN

Optic Atrophy in Suriname. By F. Hendrikse. Nijmegen, The Netherlands, Kliniek voor Vogheelkunde, Katholieke Universiteit, 1980. Paperbound, 15 black and white figures, three color figures.

Studies of the incidence of a particular disease entity in a population or area are usually done to determine whether there is a specific hereditary factor at work or whether an environmental process exists that may be producing the entity described. The author has not been able to find any hereditary factors that would explain what appears to be a high incidence of optic atrophy in Suriname. He proposes that there may be a high cyanide intake in various cassava products; however, the Indian populations also have diets with cyanogenetic ingredients and the incidence of optic atrophy was much lower in Indians than that in the other natives of Suriname. In summary, neither a hereditary factor nor an environmental factor could be implicated as an explanation for the incidence of optic atrophy in Suriname. Currently many immigrants from Suriname live in the Netherlands and it would be interesting to compare the incidence of optic atrophy in this group with the native Hollanders.

DAVID SHOCH

Advances in Ophthalmology. Volume 39. Edited by M. J. Roper, H. Sautter, and E. B. Streiff. Basel, Switzerland, S. Karger AG, 1979. Hardcover, index, 103 black and white figures. $122.75

Volume 39 of this fine international series presents six reviews by highly regarded investigators. Two excellent chapters by J. P. François contain practical clinical information regarding ocular manifestations in demyelinating diseases and the genesis and genetics of retinoblastoma.

The report of experimental animal studies on changes in the ultrastructure of the iris after irradiation with intense light by E. van der Zypen, F. Frankhauser, H. Bebie, and J. Marshall occupies nearly half of the volume. This thoroughly documented and well-illustrated review is a seminal contribution to the study of thermal (induced by continuous-wave argon ion laser) and mechanical (induced by the Q-switch ruby laser) effects of laser energy on iris tissue. Additional reviews by S. Kaldarar-Pedotti ("Die mitotische Aktivität des Pigmentephithels während der embryonalen und postembryonalen Entwicklung") P. Gysin ("Der 32P-Test in der Ophthalmologie") and M. Tsacopoulos ("Le rôle des facteurs métaboliques dans la régulation du débit sanguin rétinien") describe carefully conducted experimental studies and surveys. The first two articles are summarized in English. All articles include comprehensive bibliographies current through 1978.

For the scientist with an interest in this

subject, for the student of international ophthalmology, and for libraries of ophthalmic science and vision research, this volume is highly recommended.

BRADLEY R. STRAATSMA

SYMPOSIA

Neurotoxicity of the Visual System. Edited by William H. Merigan and Bernard Weiss. Raven Press, 1980. Hardcover, 288 pages, subject index. $32.

POTTS, A. M: **Duality of the optic nerve in toxicology**

DYER, R. S.: **Effects of prenatal and postnatal exposure to carbon monoxide on visually evoked responses in rats**

HAYREH, M. M. S., HAYREH, S. S., BAUMBACH, G. L., CANCILLA, P., MARTIN-AMAT, G., AND TEPHLY, T. R.: **Ocular toxicity of methanol. An experimental study**

SUGIMOTO, K., AND GOTO, S.: **Retinopathy in chronic carbon disulfide exposure**

RAITTA, C., AND TOLONEN, M.: **Microcirculation of the eye in workers exposed to carbon disulfide**

LEVETT, J., AND JAEGER, R.: **Effects of alcohol on retinal potentials, eye movements, accommodation, and the pupillary light reflex**

GRAMONI, R.: **Retinal function of rats exposed to organomercurials**

FINOCCHIO, D. V., LUSCHEI, E. S., KARLE MOTTET, N., AND BODY, R.: **Effects of methylmercury on the visual system of rhesus macaque** *(Macaca mulatta)*. **I. Pharmacokinetics of chronic methylmercury related to changes in vision and behavior**

SHAW, C.-M., MOTTE, N. K., AND CHEN, W. J.: **Effects of methylmercury on the visual system of rhesus macaque** (*Macaca mulatta*). **II. Neuropathological findings (with emphasis on vascular lesions in the brain**

EVANS, H. L., AND GARMAN, R. H.: **Scotopic vision as an indicator of neurotoxicity**

MERIGAN, W. H.: **Visual fields and flicker thresholds in methylmercury-poisoned monkeys**

IWATA, K.: **Neuroophthalmologic indices of Minamata disease in Niigata**

TSUTSUI, J.: **Clinical and pathological studies of eye movement disorders in Minamata disease**

COOPER, G. P., FOX, D. A., HOWELL, W. E., LAURIE, R. D., TSANG, W., AND LEWKOWSKI, J. P.: **Visual evoked responses in rats exposed to heavy metals**

BOWMAN, R. E., AND BUSHNELL, P. J.: **Scotopic visual deficits in young monkeys given chronic daily low levels of lead**

ISHIKAWA, S., AND MIYATA, M.: **Development of myopia following chronic organophosphate pesticide intoxication. An epidemiological and experimental study**

REVZIN, A. M.: **Effects of organophosphate pesticides and alcohol on visual mechanisms**

Correction

In the article, "HLA antigens in recurrent stromal herpes simplex virus keratitis" (Am. J. Ophthalmol. 89:54, 1980), by R. H. Meyers-Elliott, J. H. Elliott, W. A. Maxwell, T. H. Pettit, D. M. O'Day, P. I. Terasaki, and D. Bernoco, the following changes should be made:

On page 56, column 2, line 8: the P value of .01 becomes a P value of .15 (not .3).

On page 57, column 1, line 17: Our findings of increased HLA-DRx3 in herpes stromal keratitis may eventually prove (not keratitis prove).

ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

Acta Neurologica Scandinavica

OPTIC ATROPHY IN EXPERIMENTAL VITAMIN B_{12} DEFICIENCY IN MONKEYS. Chester, E. M., Agamanolis, D. P., Harris, J. W., Victor, M., Hines, J. D., and Kark, J. A. (Depts. Med., Pathol., Hematol., and Neurol., Cleveland Metropolitan Gen. Hosp., and Case Western Reserve Univ., Cleveland, Ohio). Acta Neurol. Scand. 61:9, 1980.

For some years there has been an entity described as nutritional amblyopia and it has been assumed that this is due to generalized starvation with an associated deficiency in the necessary vitamins. This study shows that there is at least one specific vitamin that can be implicated in optic atrophy and this is vitamin B_{12}. Visual impairment was noted in all seven of the deficient animals that were evaluated by clinical observation. Ophthalmoscopic examination disclosed optic atrophy in six of the seven deficient monkeys. Degeneration of the visual pathway was demonstrated by pathologic examination in eight of the deficient group of nine (one is still alive). Loss of ganglion cells was noted in the maculas of two of the three deficient animals with completed studies. In three control animals there were neither visual disturbances nor ophthalmoscopic changes and in two animals autopsy disclosed no lesions in the visual pathways. (7 figures, 1 table, 68 references)—David Shoch

Albrecht von Graefes Archiv für Klinische und Experimentelle Ophthalmologie

ENDOTHELIAL CELLS IN DOMINANT CORNEA GUTTATA. Vannas, A., Setälä, K., and Järvinen, E. (Eye Clin., Univ. Helsinki, Helsinki, Finland). Albrecht von Graefes Arch. Klin. Ophthalmol. 213:11, 1980.

A family with autosomal dominant cornea guttata in three generations is described. There were 25 healthy patients and six patients with cornea guttata. A few guttata were already present at an early age and very pronounced corneal endothelial guttata appeared in the middle-aged patients. No other ocular pathology was associated with this condition and the endothelial cell counts were not affected by guttata excrescences. The corneal thickness was normal in the affected and non-affected members of the family while bullous keratopathy did not seem to be associated with dominant cornea guttata in this family. The endothelial photographs support the hypothesis that there are two forms of cornea guttata. One is inherited as a dominant trait without corneal edema and the endothelial cells appear normal with specular microscopy. The other form of cornea guttata is followed by Fuchs' dystrophy. Previous literature indicates that this also has a dominant inheritance. (5 figures, 1 table, 10 references) —David Shoch

EFFECTS OF TIMOLOL MALEATE ON TEAR FLOW IN HUMAN EYES. Bonomi, L., Zavarise, G., Noya, E., and Michieletto, S. (Univ. Eye Clin., Verona, Italy). Albrecht von Graefes Arch. Klin. Ophthalmol. 213:19, 1980.

Lacrimal function was studied in 30 patients treated for glaucoma with 0.25% timolol eye drops. Rose bengal and fluorescein staining disclosed punctate epithelial defects in 11 eyes after one week. During the following weeks these defects disappeared spontaneously in most eyes. Schirmer tests I and II, tear lysozyme and pre-corneal film break-up time were significantly decreased by the treatment, while tear immunoglobulins were unimpaired. The topical timolol treatment appears to decrease tear production but this effect is quantitatively limited and does not appear dangerous for normal eyes, although it may become so for eyes with an originally low lacrimal secretion. (1 table, 14 references)—David Shoch

American Journal of Pathology

ANIMAL MODEL OF HUMAN DISEASE: RETINITIS PIGMENTOSA. Lai, Y., Jacoby, R. O., Jensen, J. T., and Yao, P. C. (Sec. Comparative Med., Yale Univ., New Haven, Conn.) Am. J. Pathol. 98:281, 1980.

There are several strains of rats that develop a retinal dystrophy but in these animals termed RCS rats the failure is of the retinal pigment epithelium to ingest terminal disks of photoreceptor outer segments. This defect results in the accumulation of outer segment material and leads to degeneration of the photoreceptor cells. The authors describe a new form of spontaneous bilateral retinal degeneration in Wag/Rij rats. This is characterized by an early onset and a slowly progressive course. Degeneration appears to begin in the photoreceptor cell body and only secondarily affects its outer segment. The phagocytic activity of the pigment epithelium remains intact. End-stage lesions include disappearance of photoreceptor cells, migration of the pigment epithelium, and disorganization of remaining retinal layers. Since in retinitis pigmentosa photoreceptor degeneration precedes alteration in pigment epithelial function, it would seem that the Wag/Rij rat lesion is a better model of retinitis pigmentosa. The Wag/Rij rats were originally obtained from the Radiobiology Institute in the Netherlands but the breeding colonies are now maintained by the Division of Animal Care at Yale University School of Medicine. (3 figures, 15 references)—David Shoch

British Journal of Ophthalmology

OPTIC DISC NEOVASCULARISATION IN DIABETIC RETINOPATHY: NATURAL HISTORY AND RESULTS OF PHOTOCOAGULATION TREATMENT. Yassur, Y., Pickle, L. W., Fine, S. L., Singerman, L., Orth, D. H., and Patz, A. (Retinal Vascular Ser., Wilmer Inst., Johns Hopkins Univ. and Hosp., Baltimore, Md.). Br. J. Ophthalmol. 64:77, 1980.

Sixty-seven patients with neovascularization and/or fibrous proliferation on the optic nerve head were observed for four years. The patients were randomly assigned for treatment with argon laser and xenon photocoagulation in only one eye, with the other eye serving as a control. Treated eyes, either with argon or xenon, had less neovascularization on the disk at the end of four years then they had before they were treated. Untreated eyes had more neovascularization at the end of the follow-up period than they had at the beginning of the study. Eyes treated with either argon or xenon had less vascularization and less fibrous proliferation at the end of the four year follow-up than untreated eyes. The increase in neovascularization is approximately three times as great in the untreated eyes as in the treated eyes. An additional benefit of treatment was the fact that fibrous proliferation on the disk in untreated eyes increased considerably while the proliferation in treated eyes increased slightly or moderately. There was no difference in the effect on disk neovascularization between argon and xenon treated eyes. (10 figures, 14 tables, 32 references)—David Shoch

PERIPHERAL RETINAL ABLATION IN THE TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY DURING PREGNANCY. Hercules, B. L., Wozencroft, M., Gayed, I. I., and Jeacock, J. (Royal Eye Hosp., Univ. Manchester, and Ahmadi Hosp., Kuwait Oil Co., Kuwait). Br. J. Ophthalmol. 64:87, 1980.

The course of proliferative diabetic retinopathy involving the optic disk was followed, and the response of peripheral retinal photocoagulation monitored by argon laser in 11 patients during and after 13 pregnancies. Traditional obstetric practice assumes that pregnancy is a stimulus to irreversible progression of proliferative diabetic retinopathy, and that timely abortion and sterilization are essential in order to achieve control of the neovascular process. Extensive photocoagulation will cause significant regression of neovascular complexes in 63% of cases, and it confers sufficient benefits to make ophthalmic indications for therapeutic abortion and sterilization no longer tenable. (8 figures, 5 tables, 18 references)—Authors' abstract

International Ophthalmology

CLINICAL EXPERIENCES WITH A SEMI-AUTOMATED PERIMETER (FIELDMASTER). Dannheim, F. (Hamburg, W. Germany). Int. Ophthalmol. 2:11, 1980.

The Fieldmaster 101 perimeter was used in 178 eyes and compared with a Tuebingen and a Goldmann perimeter. The Fieldmaster allows for a fast and relatively accurate screening test in the detection-phase of perimetry, independent of the skill of the perimetrist. This instru-

ment missed only 2.6% of all pathological fields found by the Goldmann perimeter, and 10% of defective fields taken with the Tuebingen perimeter. In one-third of the abnormal findings of the Fieldmaster the defects were even more realistic than in the plots of the Goldmann perimeter, as proven by the static and kinetic fields of the Tuebingen perimeter. A field test with a Fieldmaster took about four minutes, with a Goldmann perimeter from five to 15 minutes and with a Tuebingen perimeter from 15 to 40 minutes. In summary, the Fieldmaster perimeter is a valuable tool for rapid, relatively accurate visual field check, independent of the skill of the perimetrist. (8 figures, 2 tables, 9 references)—David Shoch

ARGON LASER TREATMENT OF RETINAL MACROANEURYSMS. van Nouhuys, E., and Deutman, A. F. (Nijmegan, The Netherlands). Int. Ophthalmol. 2:45, 1980.

The necessity of treatment of retinal macroaneurysms is still a subject of discussion since some macroaneurysms may heal without any treatment with good recovery of vision while others are the cause of lasting visual impairment. The authors present the results of treatment in six patients with retinal macroaneurysms. These patients all had macular edema. In general the results of treatment of macroaneurysms directly were good. It has been reported that the macroaneurysms disappear spontaneously following retinal hemorrhage, therefore, the authors conclude that there is no need to treat macroaneurysms if there is a retinal hemorrhage present but if there is associated posterior pole edema and particularly exudation then treatment is appropriate since it tends to hasten the absorption of the edema fluid and the exudates whose source is the macroaneurysm. (16 figures, 13 references)—David Shoch

Japanese Journal of Ophthalmology

THE ASSOCIATION OF THE HLA SYSTEM WITH OCULAR DISEASES. Ohno, S. (Dept. Ophthalmol., Hokkaido Univ., Sapporo, Japan). Jap. J. Ophthalmol. 23:355, 1979.

The HLA antigen system, the major histocompatibility complex in man, has recently been shown to play many significant biological roles. An association between the HLA system and a variety of diseases, including many important ocular diseases, is one of the most important spin-offs of recent research in this area. Within the HLA region which is on the autosomal chromosome 6, there exist five HLA loci, HLA-A, HLA-B, HLA-C, HLA-D, and HLA-DR. Some characteristic features of the HLA system is the enormous polymorphism, marked ethnic variation of the frequency of a particular antigen, and the presence of linkage disequilibrium between HLA antigens.

Up to the present, more than 30 ocular diseases have been studied for the association with HLA antigens. Significant associations with certain HLA antigens have been reported in ocular cicatrical pemphigoid, Sjögren's syndrome, adult onset iridocyclitis, Behçet's disease, Vogt-Koyanagi-Harada disease, presumed ocular histoplasmosis, Takayasu's disease, myasthenia gravis, multiple sclerosis and optic neuritis. (5 figures, 14 tables, 117 references)—Author's abstract

THE IMMUNE SYSTEM IN THE EYE AND ALLERGIC UVEITIS. Shimada, K. (Dept. Ophthalmol., Jichi Med. School, Japan). Jap. J. Ophthalmol. 23:469, 1979.

Within the eye, antibody formation takes place in a manner different from that in other tissues of an individual. Antibody-forming cells found in the eye come from outside the eye, propagate and produce antibodies, about 95% of which are IgG. Specific antibodies are detectable only in less than 20% of immunoglobulin containing cells in the intraocular tissues and the remaining 80% produce antibodies against the antigens with no relation to the antigen which provoked antibody response within the eye. Immune substances are distributed at low concentration in the intraocular tissues and immune cells are also in small number. In the normal aqueous humor, for example, the concentration of immunoglobulins is 200 times less than the level in serum and complements 1,000 times less. Large molecular proteins, eg. IgM and C1 are not detectable. On the contrary, all of the serum proteins are found at relatively high concentration in the plasmoid aqueous humor.

The increase of protein concentration in the aqueous humor in the inflamed eye is associated with severity of ocular inflammation. The author used a slit-lamp microphotometer to observe the permeability changes of the blood-

aqueous barrier. By means of this method, the effects of various pharmacological agents on ocular inflammation induced by passive Arthus reactions were examined. Cobra venom completely suppressed increased permeability of the blood-aqueous barrier in the allergic uveitis. Antihistamines are effective mainly in the early phase. Reserpine, epinephrine, indomethacin and steroid remarkably inhibited vascular responses throughout the whole processes and the latter two agents suppressed leucocyte infiltration. (8 figures, 5 tables, 30 references)—Author's abstract

Journal of the American Geriatrics Society

DIPLOPIA IN THE AGED: ETIOLOGY AND MANAGEMENT. Cinotti, A., Stephens, E., Wilcox, L., Stephens, G. M., and Caputo, A. (Dept. Ophthalmol., Eye Inst. of New Jersey, Newark, N. J., and Depts. Ophthalmol. and Orthoptics, Tufts New England Med. Ctr., Boston, Mass.). J. Am. Geriatr. Soc. 28:84, 1980.

Two series of elderly patients with diplopia from two different institutions are presented. The total number of patients is 57 and in both series of approximately equal size the most common cause of diplopia was in association with thyroid disease. Of the 57 patients this was the etiology in 21 or almost 40%. The second most common cause was tumors. It is not made clear whether these tumors were intraorbital or intracranial but the total group was about 10% of the entire patient population. The third most common cause was trauma and this occurred in five patients or roughly 10% of the group study. Suprisingly, there were only two diabetics in this group. Thus, well over 50% of an aging population with diplopia will have either thyroid disease or tumors and this is most important in directing the initial work-up of these patients. (1 figure, 1 table, 12 references)—David Shoch

Journal of the National Medical Association

CONJUNCTIVAL BIOPSY IN SARCOIDOSIS. Merritt, J. C., Lipper, S. L., Peiffer, R. L., and Hale, L. M. (Dept. Ophthalmol., Univ. North Carolina, Chapel Hill, N. C.). J. Natl. Med. Assoc. 72:347, 1980.

The clinical triad of mutton fat precipitates and nodules on the iris comprise the most common ocular presentation of sarcoidosis; conjunctival lesions are found in 50% of cases. The authors describe 16 such patients and conjunctival biopsy was positive in 12 of them. The authors suggest that excisional biopsy of the conjunctiva be performed whenever suspected sarcoid lesions are observed. The ease of performance, lack of complications and specificity of conjunctival biopsy argue that this should become a more widely used outpatient diagnostic procedure for sarcoid particularly in the southeastern United States where this disease seems endemic. (4 figures, 1 table, 7 references)—David Shoch

Journal of Pediatric Ophthalmology and Strabismus

THE RELATIONSHIP BETWEEN SOFT TISSUE ANOMALIES AROUND THE ORBIT AND GLOBE AND ASTIGMATIC REFRACTIVE ERRORS: A PRELIMINARY REPORT. Cuttone, J., Durso, F., Miller, M., and Evans, L. (Dept. Ophthalmol., Loyola Univ. Stritch School of Med., Maywood, Il.). J. Pediatr. Ophthalmol. Strabismus 17:29, 1980.

Corneoscleral limbal masses were created in ten rabbit eyes and upper eyelid colobomas were produced in an additional ten eyes. The resultant changes in corneal curvature were recorded over a one-month period using streak retinoscopy and photokeratometry. By these methods, the authors determined that forces at or near the corneoscleral limbus can produce changes in the corneal curvature that lead to refractive errors primarily of the astigmatic variety. There is a shift of the axis of astigmatism towards the meridian 90 degrees away from the external force or an increase of astigmatism along the meridian where the force was exerted. In this study, corneal curvature changed significantly in the coloboma and epibulbar mass groups when compared to the control group. This study supports a causal relationship between soft tissue anomalies and astigmatic refractive errors seen clinically in

certain syndromes, such as Goldenhar's and mandibulofacial dysostosis. These findings suggest that patients observed with periorbital soft tissue defects may be at risk for the development of unilateral anisometropic refractive errors and secondary amblyopia. Recognition of this entity is essential in order that adequate therapy can be instituted at an early age. (3 figures, 3 tables, 8 references)—Authors' abstract

Laryngoscope

THE INFLUENCE OF EMBRYOLOGY OF THE MID-FACE ON THE SPREAD OF EPITHELIAL MALIGNANCIES. Panje, W. R., and Ceilley, R. I. (Depts. Otolaryngol. and Maxillofacial Surg., and Dept. Dermatol., Univ. Iowa Hosp. and Clinics, Iowa City, Iowa). Laryngoscope 89:1914, 1979.

The authors analyzed 150 cases of epithelial cancer of the mid-face, primarily basal cell carcinoma, treated by microscopically controlled excision. Patterns of tumor spread were related to embryological fusion planes, with deep invasion within given zones before superficial spread across fusion planes. The lower eyelid lateral to the punctum arises from the maxillary mesenchymal process. The medial canthal region and lower eyelid medial to the punctum arises from the lateral nasal process. The lacrimal collecting system lies within the fusion plane between these mesenchymal processes. Of particular importance to ophthalmic surgeons is the behavior of lesions medial to the punctum, which tend to invade deeply into the lacrimal sac and periorbita before spreading lateral to the punctum. Predictability of patterns of invasion is lost after any mode of treatment (surgery, cryosurgery, irradiation) that induces fibrosis and alters the underlying connective tissue strata. (7 figures, 9 references)—Gerald J. Harris

ADENOCARCINOMA OF THE ETHMOID FOLLOWING RADIOTHERAPY FOR BILATERAL RETINOBLASTOMA. Rowe, L. D., Lane, R., and Snow, J. B. (Dept. Otolaryngol., Univ. California, San Francisco, Calif., and Dept. Otorhinolaryngol. and Human Communication, Univ. Pennsylvania, Philadelphia, Pa.). Laryngoscope 90:61, 1980.

Retinoblastoma occurs once in every 23,000 to 34,000 births and is the most common malignant intraocular tumor of childhood. Second fatal mesenchymal and epithelial primaries have been described in 8.5% of patients with bilateral retinoblastoma previously treated with radiotherapy. Papillary adenocarcinoma arising within the paranasal sinuses has not been reported so that this represents the first such case. In the patient reported here, the papillary adenocarcinoma of the ethmoid sinus arose 30 years after high-dose radiotherapy for bilateral retinoblastoma. In spite of aggressive therapy the patient died of hepatic metastases. The high incidence of second fatal primary neoplasms in patients with bilateral retinoblastomas receiving radiation suggests an innate susceptibility that may add to the risk of radiotherapy. Careful long-term head and neck surveillance is mandatory if early aggressive management of these extremely lethal tumors is to be successful. (6 figures, 29 references)—David Shoch

New England Journal of Medicine

INCREASED INCIDENCE OF RETINOPATHY IN DIABETICS WITH ELEVATED BLOOD PRESSURE. Knowler, W. C., Bennett, P. H., and Ballintine, E. J. (National Inst. of Arthritis, Metabolism and Digestive Diseases, Phoenix, Ariz.). N. Engl. J. Med. 302:645, 1980.

The incidence of retinopathy was assessed in 188 diabetic and 284 nondiabetic Pima Indian adults six years after an initial examination had shown each to be free of retinopathy. The incidence of retinal lesions was strongly related to the presence of diabetes and, among the diabetic subjects, to insulin treatment, disease duration, plasma glucose concentration, and presence of other complications such as proteinuria, loss of deep tendon reflexes, and increased vibration-sensation threshold. In diabetic subjects not taking insulin, the incidence of exudates in those with systolic blood pressures of at least 145 mm Hg was more than twice that of those with pressures of less than 125 mm Hg. This association persisted when assessed within categories of subjects stratified according to 13 potentially confounding variables, suggesting that control of blood pressure may reduce the incidence of retinal exudates in diabetics not treated with insulin. (1 figure, 4 tables, 12 references)—Authors' abstract

Ophthalmology

THE SLIPPED MUSCLE. Parks, M. M., and Bloom, J. N. (Dept. Ophthalmol., Children's Hosp. National Med. Ctr., Washington, D. C.). Ophthalmol. 86: 1389, 1979.

A slipped muscle occurs in strabismus surgery when the sutures are placed through the capsule and do not, in fact, catch the tendon. The resulting signs are similar to those of a lost muscle but less severe. There is a consecutive deviation opposite to that for which the surgery was performed and usually a limitiation of duction in the field of action of the operated muscle. At the time of reoperation the appearance is quite classic with only the capsule being attached at the site of the original operation. (4 figures, 1 reference)—David Shoch

THE EFFECTS OF CONGENITAL NYSTAGMUS SURGERY. Flynn, J. T., and Dell'Osso, L. F. (Bascom Palmer Eye Inst., Dept. Ophthalmol., Univ. Miami, Miami, Fla.). Ophthalmol. 86: 1414, 1979.

Anderson-Kestenbaum operations for congenital nystagmus with severe head turn have been employed for the past 25 years. They have been documented as being effective in correcting head turns associated with congenital nystagmus. The authors have studied a group of patients with congenital nystagmus and head turn, both preoperatively and postoperatively, by means of recordings of eye movements. They document the effect of surgery in shifting the null position, in broadening the null position, and in lowering the nystagmus intensity. In some cases, an improvement of the visual acuity has also occurred. (9 figures, 23 references)—Authors' abstract

Plastic and Reconstructive Surgery

ORBITAL CELLULITIS AND BLINDNESS FOLLOWING A BLEPHAROPLASTY. Morgan, S. C. (Pasadena, Calif.). Plast. Reconstr. Surg. 64:823, 1979.

Retrobulbar hemorrhage following blepharoplasty with resultant compression of the optic nerve and blindness is a well documented entity. However, the blindness may also occur from the orbital congestion associated with cellulitis as is described in the patient reported here. A 57-year-old woman in good health and with no evidence of any infection anywhere had a blepharoplasty, face lift, and dermabrasion performed as an outpatient. Three days later she complained of pain and discomfort and a diagnosis of cellulitis of the left orbit was made. The etiologic organism was apparently streptococcus and the patient responded slowly to therapy but vision in the eye was lost, probably from compression of the optic nerve. This is a particularly dangerous complication since the infection may extend backward to cause a cavernous sinus thrombosis, a complication which is frequently fatal. In contrast to orbital hemorrhages, incision and drainage is not often useful with cellulitis because of the diffuse nature of the process and the generalized edema of all the tisues without any localized, loculated masses. (2 figures, 15 references)—David Shoch

RESECTION OF THE PROMINENT LATERAL FAT PAD DURING UPPER LID BLEPHAROPLASTY. Owsley, J. Q. (Dept. Plastic Surg., R. K. Davies Med. Ctr., San Francisco Calif.). Plast. Reconstr. Surg. 65:4, 1980.

The presence of a lateral fat pad beneath the orbicularis muscle, which overlies the lateral orbital rim, is described in patients who have marked bagginess of the upper eyelid and a bulky hood of tissue extending well beyond the lateral canthal region. This fat is separate from the fusiform central fat pad and lies superficial to the orbital septum. Resection of a strip of orbicularis muscle and the underlying lateral fat pad, in addition to the routine removal of central and medial fat pads, provides an enhanced appearance and complete correction of the lateral hood in such individuals. (9 figures, 7 references)—Author's abstract

NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.

Send News Items double-spaced to News Editor, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, Illinois 60611

For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least four months before the date of occurrence.

TWELFTH INTERNATIONAL CONGRESS OF CHEMOTHERAPY

The Twelfth International Congress of Ophthalmology will be held in Florence, Italy, July 19-24, 1980. For further information, write Secretariat, 12th International Congress of Chemotherapy, Via della Scala, 10 50123 Florence, Italy.

VII AFRO-ASIAN CONGRESS OF OPHTHALMOLOGY

The VII Afro-Asian Congress of Ophthalmology will be held in Tunis, Tunisia, Oct. 26-29, 1980. For further information, write A. Trabelsi, General Secretary, Afro-Asian Congress of Ophthalmology, Institut d'Ophthalmologie, Bab Saadoun, Tunis, Tunisia.

ISRAEL INTERNATIONAL SYMPOSIUM ON GLAUCOMA

The Israel International Symposium on Glaucoma will be held in Tel Aviv, Israel, Sept. 3-5, 1980. For further information, write the Secretariat, Israel International Symposium on Glaucoma, P.O.B. 16271, Tel Aviv, Israel.

ALL INDIA OPHTHALMOLOGICAL CONFERENCE

The XXXX All India Ophthalmological Annual Conference will be held Jan. 10-13, 1981, in Udaipur India. For further information, write Dr. M. R. Jain, Organising Secretary, R. N. T. Medical College, Udaipur Pin-31300k, India.

XI INTERNATIONAL PIGMENT CELL CONFERENCE

The XI International Pigment Cell Conference will be held in Sendai, Japan, Oct. 14-17, 1980. For further information, write Professor Makoto Seiji, Dept. of Dermatology, Tohoku University, Sendai, Japan.

TENTH CAMBRIDGE OPHTHALMOLOGICAL SYMPOSIUM

The Tenth Cambridge Ophthalmological Symposium, The Ocular Vasculature, will be held at St. John's College, Cambridge, England, Sept. 1 and 2, 1980. For further information, write Postgraduate Medical Centre, Addenbrooke's Hospital, Hills Road, Cambridge, England CB2 2QQ.

SCHEIE EYE INSTITUTE: OCUTOME/FRAGMATOME WORKSHOP

The Scheie Eye Institute, Department of Ophthalmology of the University of Pennsylvania will sponsor an Ocutome/Fragmatome System, Symposium and Workshop, Oct. 2 and 3, 1980. The fee is $450. For further information, write Alexander J. Brucker, M.D., Course Director, Scheie Eye Institute, 51 N. 39th St., Philadelphia, PA 19104.

INTERNATIONAL EYE FOUNDATION

The International Eye Foundation needs usable slit lamps, phoropters, ophthalmoscopes, tonometers, operating microscopes, and surgical instruments for use in developing countries. The equipment is tax-deductible when sent with estimate of value to the International Eye Foundation, 7801 Norfolk Ave., Bethesda, MD 20014.

SALLY LETSON SYMPOSIUM ON GLAUCOMA

The Sally Letson Symposium on Glaucoma will be held Sept. 25 and 26, 1980, in Ottawa, Canada. For further information, write Dr. A. G. Watson, 267 O'Connor St., Suite 406, Ottawa, Canada K2P 1V3.

SOUTHERN CALIFORNIA PERMANENTE MEDICAL GROUP AND UNIVERSITY OF CALIFORNIA, SAN DIEGO: THIRD ANNUAL OPHTHALMOLOGY SYMPOSIUM

The Southern California Permanente Medical Group and the University of California, San Diego will present the Third Annual Ophthalmology Symposium, "Ocular trauma, uveitis and retinal disorders," Jan. 30 and 31, 1981, at Little America Westgate Hotel, San Diego, California. For further information, write Southern California Permanente Medical Group, Education Office, 4647 Zion Ave., San Diego, CA 92120.

INAUGURAL IDA MANN LECTURE: UNIVERSITY OF OXFORD

Morton F. Goldberg gave the inaugural Ida Mann Lecture at the University of Oxford, March 13, 1980. Dr. Goldberg was presented with the Ida Mann Medal.

Personals

Peter Y. Evans

Peter Y. Evans, has been appointed president of the Joint Commission on Allied Health Personnel in Ophthalmology in Washington, D.C.

Otto Hockwin

Otto Hockwin, professor and head of the Division of Ophthalmology, University of Bonn, Germany, is a visiting professor at Emory University, Atlanta, Georgia. The professorship is sponsored by Bausch and Lomb, Inc.

Jules Stein

The Johns Hopkins University awarded the degree of Honorary Doctor of Humane Letters to Jules Stein at the University's 102nd commencement exercises on May 30, 1980. The award is in recognition of Dr. Stein's distinguished achievements in support of ophthalmology and vision research. As founder and chairman of Research to Prevent Blindness, Inc., he has been a dominant figure in mobilizing logistical support for eye research in the nation's medical schools. Research to Prevent Blindness, Inc., is the nation's leading voluntary organization in support of eye research, to which it has channeled more than $38 million.

David Worthen

David Worthen has been appointed Assistant Chief Medical Director for Academic Affairs of the Veterans Administration. Dr. Worthen is professor and head of the Department of Ophthalmology, University of California, San Diego, and Chief, Ophthalmology Service, Verterans Administration Medical Center, San Diego.

New Research Grants Awarded By The National Eye Institute

January 1, 1980 to March 31, 1980

Research Project Grants

Institution	Principal Investigator	Title of Project	Amount Awarded
Presbyterian-University of Pennsylvania Medical Center Philadephia, Pennsylvania	Gustave D. Aguirre	Pigment epithelial hypertrophy	$ 24,130
Tennessee Technological University Cookeville, Tennessee	Barbara Albers-Jackson	Lipid metabolism of normal, aging and cataractous lens	59,124
Tulane University New Orleans, Louisiana	William Cohen	Diabetic cataract: Prevention by photoaffinity drugs	46,012
University of Puerto Rico San Juan, Puerto Rico	Sixto Garcia-Castineiras	Structural biochemistry of lens color and flourescence	98,397
Medical College of Georgia Augusta, Georgia	James M. Hill	Iontophoresis of antivirals to herpes eye infections	80,229
California Institute of Technology Pasadena, California	Takuji Kasamatsu	Monoaminergic control of developing visual neurons	93,974
University of Utah Salt Lake City, Utah	Helga E. T. Kolb	Neural circuitry of the vertebrate retina	134,990
University of California Berkeley, California	Robert B. Mandell	Oxygen requirement for continuous-wear contact lenses	55,521
University of North Carolina Chapel Hill, North Carolina	John C. Merritt	Cannabinoids' effect on intraocular and blood pressure	74,299

Institution	Principal Investigator	Title of Project	Amount Awarded
Oakland University Rochester, Michigan	Kazem M. Mostafapour	Beta-crystallins in normal and cataractous lenses	66,403
Purdue University West Lafayette, Indiana	William L. Pak	Mechanism of prolonged excitation in photoreceptors	45,430
Johns Hopkins University Baltimore, Maryland	Arthur M. Silverstein	The pathogenesis of trachoma	177,856
Presbyterian-University of Pennsylvania Medical Center Philadelphia, Pennsylvania	Stephen H. Sinclair	Blue field entoptic test and macular circulation	63,380
University of California San Francisco, California	Walter H. Stern	Experimental massive periretinal proliferation	99,069
Eye and Ear Hospital of Pittsburgh Pittsburgh, Pennsylvania	Cholappadi V. Sundar Raj	The corneal epithelial basement membrane	88,948
University of Miami Miami, Florida	Gail S. Tucker	Anatomic changes in the aging mammalian retina	58,390
University of Mississippi University, Mississippi	Coy W. Waller	Cannabinoids in the treatment of glaucoma	117,455
University of California, San Diego La Jolla, California	David M. Worthen	Argon laser trabeculotomy study	46,479
Georgia Institute of Technology Atlanta, Georgia	Leon H. Zalkow	Antiglaucoma compounds from *Cannabis sativa*	94,200

National Research Service Award Fellowships

Institution	Principal Investigator	Title of Project	Amount Awarded
University of Missouri Columbia, Missouri	Graig E. Eldred	O^2-mediated mechanisms in outer segment disposal	$ 15,535
U.S. National Institutes of Health Bethesda, Maryland	Judith A. Evans	Dopamine-containing neurons in rabbit retina	12,960
Yeshiva University New York, New York	David R. Friedlander	Retinotectal specificity in fetal mouse co-cultures	15,535

Research Career Development Awards/Academic Investigator Awards

Institution	Principal Investigator	Title of Project	Amount Awarded
Estelle Doheny Eye Foundation Los Angeles, California	Janet C. Blanks	Retinal differentiation, cell interactions, & plasticity	$ 28,620
Harvard University Boston, Massachusetts	Peter R. MacLeish	Photoreceptor transduction and retinal synapse formation	31,444

INSTRUCTIONS TO AUTHORS

For the preparation of manuscripts for THE AMERICAN JOURNAL OF OPHTHALMOLOGY

THE AMERICAN JOURNAL OF OPHTHALMOLOGY publishes original and timely articles dealing with clinical and basic ophthalmology. Every typescript submitted is evaluated by two or more scientific referees who recommend that the paper be (1) accepted as submitted, (2) returned for revision, or (3) rejected. Acceptance is determined by such factors as the originality, significance, and validity of the contribution; the suitability of the subject matter for subscribers of THE JOURNAL; and the editorial care with which the manuscript has been prepared. Manuscripts that require extensive editorial correction or mechanical preparation will be returned for that purpose.

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Single spacing should not be used anywhere in the manuscript. The entire manuscript—including title page and footnotes, text, acknowledgments, references, tables, and legends—should be double spaced. Vertical lines and underlining should not be used anywhere in the text, references, tables, or legends. See the section on tables for the use of horizontal lines.

Submit an original and at least one duplicate copy of both the typescript and the figures. Xerographic duplicates of the typescript are preferred to carbon copies.

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1. Title page
2. Text and summary
3. Acknowledgments
4. References
5. Tables
6. Legends for figures

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Published acknowledgment requires an exceptional and conspicuous contribution different from that which occurs with the preparation of every paper printed in THE JOURNAL. Thus, acknowledgments will be published rarely.

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1. Fuxe, K., and Jonsson, G.: The histochemical fluorescence method for the demonstration of catecholamines. Theory, practice and application. J. Histochem. Cytochem. 21:293, 1973.

2. Bjorklund, A., Flack, B., and Owman, C.: Fluorescence microscopic and microspectrofluorometric techniques for the cellular localization and characterization of biogenic amines. In Berson, S. A. (ed.): Methods in Investigative and Diagnostic Encocrinology, vol. 1. London, North-Holland Publishing Co., 1972, p. 318.

3. Duke-Elder, S., and Leigh, A. G.: Diseases of the Outer Eye. Cornea and Sclera. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 8, pt. 2. St. Louis, C. V. Mosby, 1965, pp. 811-856.

Abbreviations of periodicals are listed in Index Medicus: Am. J. Ophthalmol.; Surv. Ophthalmol.; Br. J. Ophthalmol; and the like. If there is any doubt about an abbreviation, the name of the publication should be spelled out completely.

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Fig. 1 (Jones, Smith, and Brown). Histologic section of the eye (hematoxylin and eosin, ×70).

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A Manual of Style, 12th ed. Chicago, University of Chicago Press, 1969.

Strunk, W., Jr., and White, E. B.: The Elements of Style, 3rd ed. New York, Macmillan Co., 1979.

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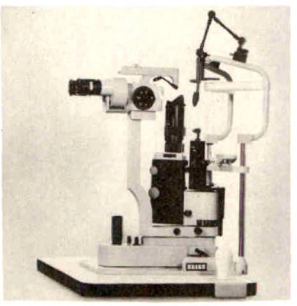

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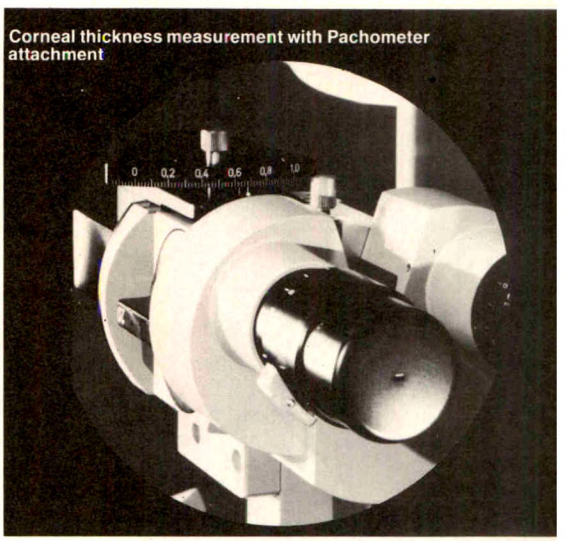
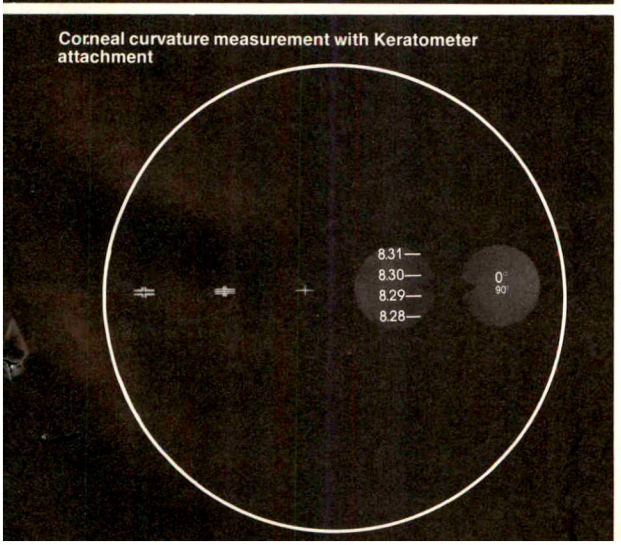
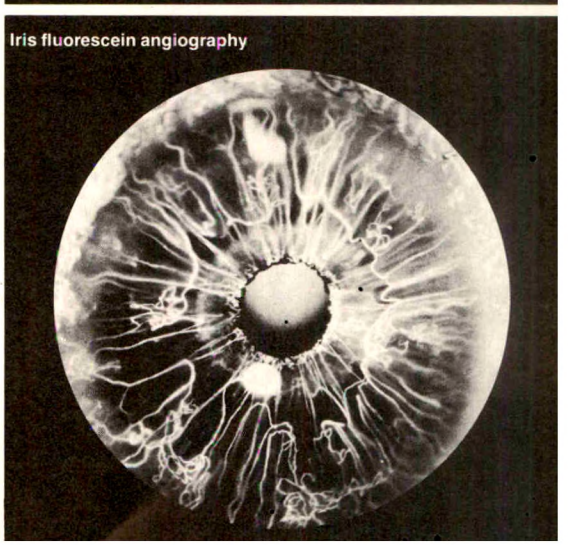






Intraocular Microsurgery Symposium and Workshop-Update Including the OCUTOME and FRAGMATOME TECHNIQUE

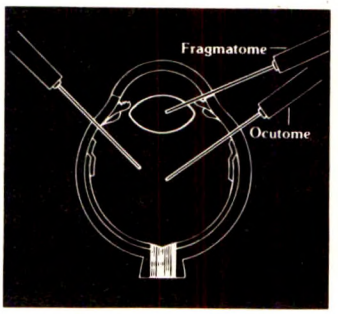
sponsored by the Retinal Vascular Department
Ingalls Memorial Hospital, Harvey, Illinois (Chicago suburb) July 25-26, 1980

This two-day symposium and workshop is designed for *both* the anterior segment and retinal-vitreal surgeon.

The symposium is specifically designed for those surgeons who already have micro-surgical experience in phacofragmentation and pars plana vitrectomy. In addition, there will be an update of material by a distinguished faculty for those who have taken previous Ocutome/Fragmatome courses.

The workshop will consist of practical microsurgical experience on animal eyes.

Registration is limited for both the symposium and workshop sections.



Faculty
Thomas M. Aaberg, M.D., Milwaukee
Steve Charles, M.D., Memphis
Gil Grand, M.D., St. Louis
Lee Jampol, M.D., Chicago
Howard Joondeph, M.D., Detroit
Ronald G. Michels, M.D., Baltimore
David H. Orth, M.D., Chicago and Harvey
Lawrence J. Singerman, M.D., Cleveland
Joel Sugar, M.D., Chicago

Course fees:

Symposium and workshop – $400.00. Includes two lunches and dinner.

Symposium only – 2 morning sessions – $150.00. Includes two lunches.

For information contact:

David H. Orth, M.D., Course Director; or
Sue Rigik, Registrar
Retinal Vascular Department
Ingalls Memorial Hospital
One Ingalls Drive
Harvey, Illinois 60426
(312) 333-2300, extension 5811

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Lawrence J. Singerman, M.D.
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Registration Fee: $450.00 physicians (limited enrollment), $150.00 lectures without workshop.

Information: Contact Alexander J. Brucker, M.D., Course Director, Scheie Eye Institute, 51 N 39th Street, Philadelphia., PA 19104, (215) 662-8675.

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Venezuelan Society in Ophthalmology.

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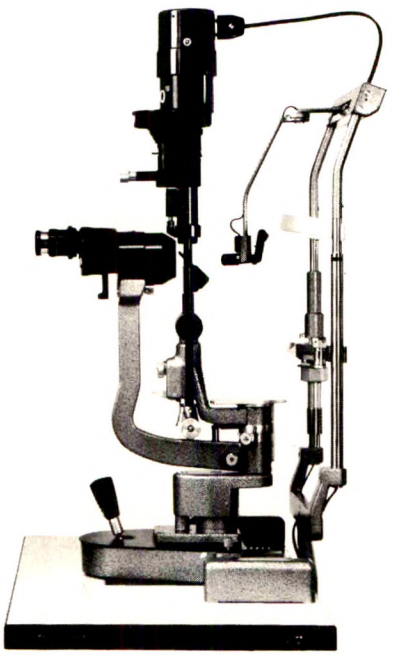

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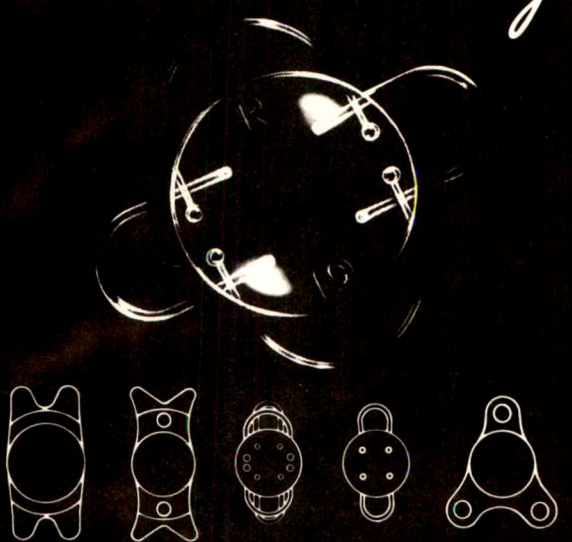

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sponsored by The Department of Ophthalmology
St. Luke's Hospital,
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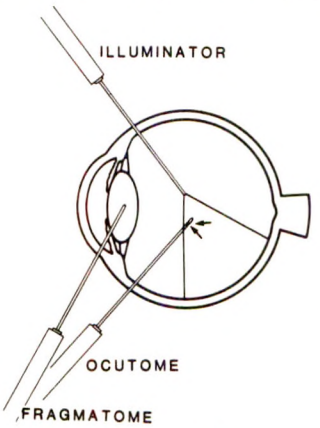

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The program topics will cover basic concepts of pars plana intraocular surgery, including indications for and techniques of pars plana lensectomy and vitrectomy. Ocutome and Fragmatome techniques will be emphasized.

16 CME Credit hours AMA Category I.

Registration Fee
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For information contact:
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(216) 421-1213

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Philadelphia
Yale Fisher, M.D.
New York
Howard Joondeph, M.D.
Detroit
Howard Kohn, M.D.
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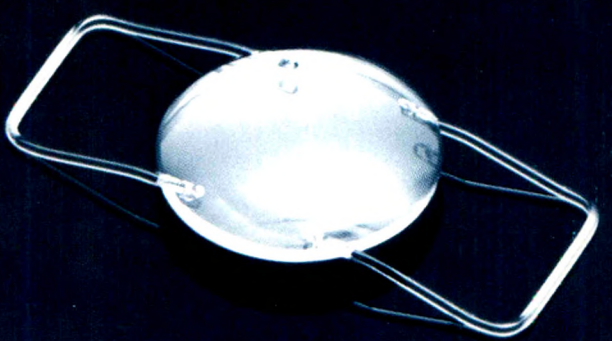

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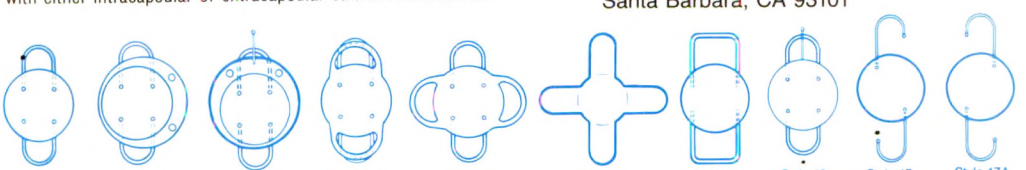

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